UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

AZURITY PHARMACEUTICALS, INC.,
Petitioner,

v.

HELSINN HEALTHCARE S.A.,
Patent Owner.

Patent No. 8,623,826
Patent No. 9,186,357
Patent No. 9,943,515
Patent No. 10,828,297

DECLARATION OF STEPHEN J. PEROUTKA, M.D., PH.D.

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I, Stephen J. Peroutka, declare as follows:

I. QUALIFICATIONS

1. I have been retained on behalf of Azurity Pharmaceuticals, Inc. (Azurity) to provide opinions based on my skills, knowledge, training, education, and experience and my examination of the materials cited herein.

2. I received my A.B. degree in neurobiology and psychology from Cornell University in 1975, where I was a College Scholar in the School of Arts and Sciences and graduated Phi Beta Kappa. In 1979, I received an M.D. degree from the Johns Hopkins University School of Medicine. I earned my Ph.D. from the Department of Pharmacology and Experimental Therapeutics at the Johns Hopkins University School of Medicine in 1980.

3. From 1980-1981, I served as an intern in the Department of Internal Medicine at Stanford University Hospital. I returned to the Johns Hopkins Hospital from 1981-1984 to complete my residency and fellowship. From 1988-1990, I served as Chief Physician of the Neurology Service at the Palo Alto Veteran's Administration Hospital. I also conducted research and taught at Stanford University as an Assistant Professor from 1984-1990.

4. I also have extensive experience working in the biotechnology and pharmaceutical industries. I served as the Vice President, Global Therapeutic Area Head of Neuroscience at Pharmaceutical Product Development, Inc. ("PPD") from

2017-2024, that became a clinical research subsidiary of Thermo Fisher Scientific in 2021. From 2016-2017, I was the Vice President, Global Therapeutic Area Head of Neuroscience and Pain at inVentiv Health Clinical. I served as Chief Medical Officer of Semnur Pharmaceuticals, Inc. from 2013-2015, where I was responsible for all medical activities including relevant pre-clinical, clinical, and regulatory affairs of the company. Prior to that role, I served as Executive Vice President and Chief Medical Officer of NeurogesX, Inc. from 2011-2013. I have founded two companies: Spectra Biomedical, Inc. and Synergia Pharma, Inc. In the past, I served as the first Director of Neuroscience at Genentech, Inc. from 1990 to 1993. As another example, I was the Vice President of the Central Nervous System group at PRA International, as a therapeutic expert providing advice and support to both the operations and business development groups. I have also served as a consultant to several companies and assisted with various aspects of these companies' product portfolios directed to treatment of neurological conditions. Since November 2024, I have been an independent clinical consultant.

5. I have extensive experience in the fields of pharmacology and clinical research. My research includes publications involving chemotherapeutic agents and antiemetic agents, such as 5-hydroxytryptamine-3 ("5-HT_3") receptor inhibitors. I also have experience with combinations of drugs to influence multiple receptors, including for improved control of emesis.

6. During my career, I have received a number of awards and honors for my work. For instance, in medical school, I won the Sandoz Award for excellence in the field of Pharmacology and the Syntex Award for Receptor Pharmacology. In 1991, I was invited to the Scientific Advisory Board of the Palo Alto Institute for Molecular Medicine. I also received the Max Hamilton Memorial Prize for significant contributions to the field of Psychopharmacology from the Collegium Internationale Neuro-Psychopharmacologicum. Many of my numerous awards and honors are summarized in my curriculum vitae (CV), which is attached as EX1020.

7. I have published my work extensively, having been named as author or co-author on over 400 articles, books, book chapters, and abstracts. In addition, I have served as an editor or referee and on the editorial boards of numerous peer-reviewed journals in my field, including *Molecular Pharmacology*, *Science*, *New England Journal of Medicine*, *Journal of Neuroscience*, *Biochemical Pharmacology*, *Clinical Neuropharmacology*, *Drugs*, *Journal of Pharmacology and Experimental Therapeutics*, and *European Journal of Pharmacology*. I currently serve on the editorial board of *Molecular Diagnosis & Therapy*.

II. SCOPE OF WORK

8. I understand from Azurity's counsel that petitions are being filed with the United States Patent and Trademark Office for Inter Partes Review of U.S. Patent Nos. 8,623,826 ("the '826 patent", EX1001), 9,186,357 ("the '357 patent",

EX1002), 9,943,515 ("the '515 patent", EX1003), and 10,828,297 ("the '297 patent", EX1004), each to Fabio Trento et al., and each entitled "Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting." I understand that each of the '826, '357, '297, and '515 patents are assigned to Helsinn Healthcare S.A. ("Helsinn").

9. I have been retained by Azurity Pharmaceuticals, Inc. ("Azurity") to offer an expert opinion on the validity of claims 1-25 of the '826 patent, claims 1-62 of the '357 patent, claims 1-23 of the '297 patent, and claims 1-23 of the '515 patent. I receive $800 per hour for my services. No part of my compensation is dependent on my opinions, and I have no financial interest in the outcome of this proceeding.

10. I have been specifically asked to provide my opinion on the unpatentability of claims 1-25 of the '826 patent, claims 1-62 of the '357 patent, claims 1-23 of the '297 patent, and claims 1-23 of the '515 patent as of November 18, 2009 (the earliest claimed priority date for each patent, which Azurity's counsel advises me is sometimes called the critical date). In connection with this analysis, I have reviewed each of the '826, '357, '297, and '515 patents. I have also reviewed and considered other documents in arriving at my opinions and cite them in this declaration.

III. LEGAL STANDARDS

11. I understand from Azurity counsel that the United States Patent and Trademark Office may cancel issued claims of the ’826, ’357, ’297, and ’515 patents if the Petitioner (here, Azurity) demonstrates that the claims fail to satisfy the requirements of patentability that the claims must be novel and non-obvious. I understand that the claims should be understood according to their ordinary and customary meaning as understood by a person having ordinary skill in the art (“POSA”) at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have been provided a copy of the prosecution history of the ’462 patent application (EX1005), the ’927 patent application (EX1006), the ’050 patent application (EX1008), and the ’327 patent application (EX1007), which issued as the ’826, ’357, ’297, and ’515 patents, respectively.

A. Anticipation

12. I understand that anticipation requires disclosure in a single reference of every element of a claim as arranged in the claim. I understand that the disclosure may be express but that it also may be satisfied by inherency when the element is necessarily present in the reference despite an absence of express disclosure. I understand that prior art disclosure of a species anticipates a genus that encompasses the species, that prior art disclosure of a point in a claimed range

anticipates the claimed range, and that prior art disclosure of a range overlapping with a claimed range anticipates the claimed range (where nothing critical has been demonstrated about the claimed range). In other words, if the prior art discloses a range that overlaps with the claimed range, the claimed range is anticipated unless the patent describes something particularly unique or critical about the specific claimed range.

B. Obviousness

13. I understand that a claimed invention is unpatentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a person having ordinary skill in the art by the critical date.

14. It is further my understanding that a determination of obviousness requires inquiries into: (1) the scope and content of the prior art when the invention was made; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent it exists, (4) objective evidence (secondary considerations) the patent owner asserts to prove the claims are not obvious despite what the prior art might suggest (*see* Sections V, XXXI, below).

15. I understand that a claim is obvious if all of the claimed elements were known in the prior art and one skilled in the art would have had reason to

combine (or modify) the elements as claimed with a reasonable expectation of success. I understand that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single prior-art reference to create the patented invention or by combining teachings of two or more prior art references. I understand that, in order for a claimed invention to be considered obvious based on a combination of prior art references, there must be some rational underpinning for the proposed combination. I understand that improper hindsight, which incorporates the unique teachings of the patent, must not be used when determining whether a person having ordinary skill in the art would make the proposed combination. Thus, a conclusion of obviousness must be firmly based on prior-art knowledge and the skill of a person having ordinary skill in the art at the time the invention was made without the improper use of post-filing knowledge.

16. In determining whether a particular combination of prior art teachings would have been obvious, I understand that the following are examples of approaches and rationales that may be considered:

(a) Combining prior art elements according to known methods to yield predictable results;

(b) Simply substituting one known element for another to obtain predictable results;

(c) Using a known technique to improve similar devices (methods, or products) in the same way;

(d) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;

(e) Applying a technique or approach that would have been "obvious to try" (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);

(f) Appreciating known work in one field of endeavor that may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or

(g) Following some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art teachings to arrive at the claimed invention.

17. I understand that obviousness may be established by showing that all of the claimed elements were known in the prior art and that a person skilled in the art would have combined the elements as claimed by known methods with no change in their respective functions, and the combination would have yielded nothing more than predictable results to one of ordinary skill in the art.

C. Secondary Considerations of Nonobviousness

18. With regard to secondary considerations of nonobviousness, I understand that objective evidence may be considered as an indication that the claimed invention would not have been obvious at the time the claimed invention was made. I understand that the purpose of secondary considerations is to prevent an improper hindsight analysis of the obviousness of the claims.

19. I also understand that there are several factors that may be considered as secondary considerations. These factors include commercial success of the invention, industry praise for the invention, skepticism of the invention, licensing of the invention, copying of the invention, long-felt need that the invention solved, failure of others, and unexpected results of the invention.

20. I understand that, in order for evidence of secondary considerations to be significant, there must be a sufficient nexus between the claimed invention and the evidence of secondary considerations. I understand that this nexus must provide a link between the merits of the claimed invention and the evidence of secondary considerations provided.

IV. OVERVIEW OF THE PATENTS

21. I have reviewed each of the ’826, ’357, ’297, and ’515 patents in its entirety including the specification, the figures, and the claims. The title of each of

these patents is "Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting." The Abstract of the '826 patent states:

> Provided are methods for treating nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery, comprising the co-administration of netupitant, palonosetron and dexamethasone.[1]

EX1001 ('826 patent), Abstract. Similarly, each of the Abstracts for the '357, '297, and '515 patents state:

> Provided are compositions and methods for treating or preventing nausea and vomiting in patients undergoing chemotherapy, radiotherapy, or surgery.

EX1002 ('357 patent), Abstract; EX1004 ('297 patent), Abstract; EX1003 ('515 patent), Abstract.

22. The common specification shared by all four challenged patents admits that combination antiemetic therapy for patients undergoing chemotherapy was well known in the prior art. For example, the specification admits that 5-HT_3 receptor antagonists, such as palonosetron, were commonly administered with dexamethasone for anti-emesis therapy. Specifically, the specification states:

> With the development of the 5-HT_3 antagonist in the early 1990s,

[1] Throughout my Declaration, I have omitted internal citations from quotes unless otherwise stated.

> there emerged new strategies in the medical community to better control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), Surgery (PONV), and radiation therapy (RINV). When added to steroids such as dexamethasone, several 5-HT_3 antagonists have been demonstrated to significantly improve the standard of life for patients undergoing emetogenic medical procedures. Examples of 5-HT_3 antagonists include ondansetron, marketed by GlaxoSmithKline, and palonosetron, developed by Helsinn Healthcare.

EX1001, 1:29-38.[2] Citing publications dating back to 2004 disclosing the beneficial effects of palonosetron, the specification further admits that palonosetron was known as a useful antiemetic when used alone or in combination with dexamethasone. *Id.*, 1:39-2:5 ("Palonosetron hydrochloride has recently emerged as a highly efficacious anti-nauseant and anti-emetic agent. See PCT publications WO 2004/045615 and 2004/073714 from Helsinn Healthcare."); *id.*, 1:29-38 (5-HT_3 antagonists combined with dexamethasone "demonstrated to significantly improve" antiemetic effect).

23. The specification discusses at length the use of centrally-acting neurokinin-1 ("NK_1") receptor antagonists, particularly netupitant, to treat nausea

[2] Representative citations are provided for the '826 patent and corresponding disclosure may be found the other three challenged patents.

and vomiting such as those induced by highly emetogenic chemotherapy (i.e., chemotherapy-induced nausea and vomiting). *E.g.*, 1001 (the ’826 patent), 2:6-28. But the specification also indicates that the invention is not netupitant; nor is it strictly limited to netupitant. For example, the specification admits that netupitant already was known in the field before the critical date. *Id.*, 2:65-3:23 (citing, amongst others, EX1014 (Bös) (US 6,297,375), which issued Oct. 2, 2001). Additionally, the specification does not limit its purported invention to netupitant. Instead, the specification asserts there are benefits to combining palonosetron with “netupitant ***or another NK1 antagonist***.”[3] *Id.*, 5:5-12; *see also id.*, 5:51-55 (“This versatility and stability is accomplished by formulating ***the NK1 antagonist*** and palonosetron in separate dosage forms….”); 5:55-58 (“the netupitant ***or other NK1 antagonist*** formulated in a tablet”). The specification explicitly declares “the invention provides versatile ***combined*** oral dosage forms of ***palonosetron and an NK_1 antagonist*** that can be readily modified depending on the therapeutic objective, and that do not present issues of stability and degradation.” *Id.*, 11:12-

[3] Bold-italics emphasis added by me throughout unless noted otherwise. Red boxes and colored highlight annotations added by me throughout unless noted otherwise.

16. Thus, the specification teaches a general ***combination*** of palonosetron with ***any*** NK_1 receptor antagonist.

24. The specification admits that aprepitant, in particular, had been used for antiemetic therapy, but asserts that the ***combination*** of palonosetron with netupitant provided improved antiemetic therapy as compared to using aprepitant alone. *Id.*, 2:6-28; *id.*, 2:29-37 ("While aprepitant has demonstrated some effect against nausea, its effects have been inconsistent."). But the specification illustrates that administering aprepitant in combination with another 5-HT_3 receptor antagonist (ondansetron) provides substantially similar results as the combination of netupitant and palonosetron. *Id.*, 16:61-20:42 & Table 5, Table 6.

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

Id., Table 6 (emphasis added) ("Aprepitant Regimen" was a standard combination of aprepitant, ondansetron, and dexamethasone; each "Palo + Netu" was a combination of netupitant, palonosetron, and dexamethasone). The specification's own data thus indicate that the antiemetic efficacy of the (known, prior art)

combination of the NK_1 receptor antagonist aprepitant and 5-HT_3 receptor antagonist ondansetron was essentially equivalent to the combination of netupitant and palonosetron, each respectively administered in combination with dexamethasone.

25. The specification never provides an apples-to-apples comparison of netupitant-plus-palonosetron to aprepitant-plus-palonosetron and therefore never shows any particular benefit for using netupitant in the combination in place of aprepitant. The specification (Table 6) presents data from the patent's study evaluating netupitant-plus-dexamethasone-plus-palonosetron and juxtaposes it with data taken from a different study involving aprepitant—Grunberg (EX1035). *Id.*, 5:2-5, 17:65-67. But the Grunberg study differed significantly and materially from the study in the specification. *See generally* EX1035 (Grunberg). First, the participants of Grunberg's study "could receive scheduled mildly or minimally emetogenic chemotherapy (Hesketh Level 1-2) during the remainder of the study period," which would cause additional emesis. EX1035 (Grunberg), 591. In contrast, the specification does not describe any additional emetogenic chemotherapy was permitted after the initial chemotherapy, only describing highly emetogenic cisplatin as administered at the beginning (on Day 1). EX1001, 17:3-18:33. Second, Grunberg did not administer the FDA-approved dose of aprepitant on Day 1 (125 mg). EX1013 (MASCC), Table 3; EX1016 (Herrington), 2081

(FDA regimen). Instead, Grunberg investigated the effect of administering a large dose of aprepitant, combining the doses of Day 1-3 into a single administration (285 mg) on Day 1. EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient single-day three-drug antiemetic regimen…. Prior to chemotherapy, patients received ***a single dose of aprepitant 285 mg*** p.o., dexamethasone 20 mg p.o., and palonosetron 0.25 mg i.v."). The specification fails to account for how such a large single dose of aprepitant might induce nausea and vomiting, such as whether adverse events (including nausea and vomiting) could arise due to the large dose. *See, e.g.*, EX1037 (Hesketh), 4116-4117 (nausea is an adverse event of aprepitant, but not evaluated as such until after 120 hours). Third, Grunberg administered the antiemetic agent dexamethasone only in a single prophylactic dose on the first day prior to administration of the chemotherapeutic agent. EX1035 (Grunberg), 590-591 ("Patients received aprepitant 285 mg p.o. and ***dexamethasone 20 mg*** p.o. 1 h prior and palonosetron 0.25 mg i.v. 30 min prior to scheduled Day 1 chemotherapy."); *id.*, Abstract ("patients received ***a single dose of*** aprepitant…***dexamethasone***…and palonosetron"). In contrast, each of the specification's other study groups received the antiemetic dexamethasone administered on each of day one, day two, day three, ***and*** day four. EX1001, 17:19-64. Each of these differences precludes making a direct comparison between Grunberg's results and the specification's results because such a flawed

comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination.

26. The patent specification's flawed comparison of Grunberg's data to the specification's data is evidenced by, for example, the ***higher*** nausea observed in Grunberg for the combination of aprepitant-plus-dexamethasone-plus-palonosetron than what the specification reported for dexamethasone-plus-palonosetron ***without any NK_1 receptor antagonist***. EX1035 (Grunberg) (percentage of patients without particular measure of nausea: 32%, 59%, 41%, 56%, 79%, and 59%); EX1001 ('826 patent), Table 6 (50.7%, 75.0%, 53.7%, 79.4%, 93.4%, and 80.9%). The specification provides no reason to conclude that adding aprepitant to dexamethasone and palonosetron would reduce the efficacy of the dexamethasone and palonosetron. Indeed, such an assumption is contradicted by Grunberg's reports that, like prior studies of the antiemetic combination of aprepitant-plus-dexamethasone-plus-palonosetron "[e]xcellent control of nausea was also achieved" when Grunberg used this combination. EX1035 (Grunberg), 593.

27. Excellent control of nausea was also achieved with the prior art aprepitant-plus-dexamethasone-plus-ondansetron combination, as recognized by Table 6 of the '826 patent:

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

EX1001 (’826 patent), Table 6. The aprepitant-ondansetron-dexamethasone combination (“Aprepitant Regimen”) showed comparable efficacy with the netupitant-palonosetron-dexamethasone treatments, and even improved efficacy as compared to low-dose netupitant. As explained above, the specification never discloses an equivalent study measuring palonosetron and netupitant with

palonosetron and aprepitant, and therefore no particular benefit for netupitant specifically was shown therein.

V. PROSECUTION HISTORY OF THE PATENTS

28. I understand from the face of each of the ’826, ’357, ’297, and ’515 patents that all belong to the same patent family, stemming from International Patent Application No. PCT/US2010/057192 and claiming priority to provisional applications US 61/382,709 and US 61/262,470 (filed on September 14, 2010, and November 18, 2009, respectively). EX1001, (63), (60); EX1002, (63), (60); EX1003, (63), (60); EX1004 (63), (60). For purposes of my opinions, I have assumed that the claims are entitled to a priority date of November 18, 2009.

A. US 8,623,826

29. During prosecution of U.S. App. No. 13/077,462, which issued as the ’826 patent, I read that the examiner asserted references against the patent applicant. EX1005 (file history of ’462 application). Specifically, the examiner stated the claimed invention was obvious over Reddy (EX1021), which taught the treatment of chemotherapy-induced nausea and vomiting by administration of an NK_1 antagonist (aprepitant) with a 5-HT_3 antagonist and dexamethasone. EX1005 (file history of ’462 application), 280-286. Reddy described that the 5-HT_3 antagonist combined with dexamethasone was the “standard of care for highly emetic chemotherapy” and described the addition of an NK_1 antagonist for

treatment. *Id.* Reddy also discloses netupitant as a suitable NK_1 antagonist that could be used in place of aprepitant. *Id.* The examiner noted that "Reddy teaches **enhanced** treatment of CINV with the addition of aprepitant or casopitant. Accordingly, the artisan would have reasonably expected enhanced treatment of CINV with netupitant." *Id.* (emphasis original).

30. I understand that the examiner stated that Reddy was not "anticipatory insofar as netupitant is not a preferred species" but nonetheless recognized that "it would have been obvious to select netupitant given its plain enumeration in the prior art reference." EX1005 (file history of '462 application), 285.

31. In response, the applicant submitted an affidavit reporting alleged unexpected results (in particular, synergy) from combining netupitant with palonosetron. EX1005 (file history of '462 application), 341-350. The affidavit was authored by an inventor of the patent application and an employee of the applicant. As I detail below, it is my opinion that the applicant never showed any alleged synergy to exist, much less within the context of the claims. Section XXXI, below (no unexpected benefits).

32. Nonetheless, the examiner allowed the application solely in view of this affidavit. The examiner stated in the reasons for allowance, in full:

> The following is an examiner's statement of reasons for allowance:
> 132 Declaration, filed 5/17/2013, affiant showing evidence of synergy (unexpected result) from the combination of netupitant and

palonosetron in regard to the claimed method.

EX1005 (file history of ’462 application), 369. As I detail further below, it is my opinion that the examiner’s reliance on the affidavit was in error, and thus the reasons for allowance were also in error.

B. US 9,186,357

33. During prosecution of U.S. App. No. 14/069,927, which issued as the ’357 patent, I read that the sole rejection against the patent application was a “nonstatutory obviousness-type double patenting” over the ’826 patent. EX1006 (file history of ’927 application), 235. I understand that the examiner rejected the claims because they “are not patentably distinct” from the claims in the ’826 patent “because they both claim a method of treating nausea and vomiting (CINV) by administering netupitant and palonosetron.” *Id.*

34. In response, the applicant added numerous dependent claims (corresponding with ’357 patent claims 17-62) and filed a terminal disclaimer. *Id.*, 292-304.

35. I understand the patent examiner allowed the application with no further rejection and without providing any reasons for allowing the claims. *Id.*, 331.

C. US 9,943,515

36. During prosecution of U.S. App. No. 15/003,327, which issued as the '515 patent, there were multiple Office action rejections. In the first rejection, I read that the examiner asserted references against the patent applicant. EX1007 (file history of '327 application), 146-152. Specifically, the examiner stated the claimed invention of then-pending claims 16, 17, 23, 24, 26, and 52 was anticipated by Reddy (EX1021), which taught the treatment of chemotherapy-induced nausea and vomiting by administration of an NK_1 antagonist (aprepitant) with a 5-HT_3 antagonist and dexamethasone. Reddy described that the 5-HT_3 antagonist combined with dexamethasone was the "standard of care for highly emetic chemotherapy" and described the addition of an NK_1 antagonist for treatment. *Id.* Reddy also disclosed netupitant as a suitable NK_1 antagonist that could be used in place of aprepitant. *Id.* The examiner also stated the claimed invention of then-pending claims 16-18, 21, 23-26, and 52-56 was obvious in view of Reddy. EX1007 (file history of '327 application), 149. The examiner explained:

> Reddy et al. teaches **netupitant** as a suitable NK-1 antagonist, it would have been obvious to use netupitant as the NK-1 antagonist in combination with 5-HT3 antagonist and dexamethasone, especially since success was found with another NK-1 antagonist, Casopitant, in combination with 5-HT3 antagonist and dexamethasone. Specifically, Reddy teaches **enhanced** treatment of CINV with the addition of aprepitant or casopitant.

Id., 149 (emphasis original).

37. The examiner also rejected the claims "on the ground of nonstatutory double patenting as being unpatentable over claims 1-25" of the '826 patent (*id.*, 150), claims 1-62 of the '357 patent (*id.*, 151), and claims 1-12 of U.S. 9,271,975 (*id.*). Further, the examiner objected to then-pending claim 17 as being an improper dependent claim "for failing to further limit the subject matter of a previous claim."

38. I understand that in the first rejection, the examiner explained that "the recitation 'wherein said netupitant occupies at least 80% of NK1 receptors in the striatum' is interpreted as ***an inherent property of netupitant***." *Id.*, 150.

39. In response, the applicant amended the independent claims to recite "wherein said therapeutically effective dose comprises a single dose of netupitant or a pharmaceutically acceptable salt thereof administered on day one of said five consecutive days." *Id.*, 196; *see also id.*, 197 (claim 54) (similar). The applicant argued that "Reddy does not anticipate or render obvious independent claims 16 and 54 because Reddy does not teach or suggest the prevention of emesis during the acute phase by netupitant" because aprepitant allegedly had a lesser effect based on Table 6 of the applicant's specification. *Id.*, 201-202. The applicant also argued that Reddy "does not describe or suggest the administration of a single dose of netupitant over a five-day period" and that "[a] tremendous amount of work was

required to discover [the] dosing limitations" of the claims. *Id.*, 200-202. The applicant then argued that its single dose of netupitant for acute and delayed phase treatment and the ability of netupitant to treat emesis during the acute phase were unexpected results. *Id.*, 203. Finally, the applicant stated it had submitted terminal disclaimers to address the obviousness-type double patenting rejections. *Id.*, 203-204. However, I note that the applicant appears to have not submitted said terminal disclaimers at that time, and the examiner repeated these rejections in the next Office action.

40. In its response to the non-final Office action, the applicant did not disagree with the examiner's contention that netupitant occupancy of NK_1 receptors in the striatum is an inherent property. Instead, the applicant argued that this property accounted for "the requirement for only a single administration of netupitant during a five-day period and might also account for netupitant's efficacy during the acute phase," contending this feature was also an "unexpected result" that supported patentability. *Id.*, 203.

41. The examiner issued a second, final Office action. *Id.*, 210-219. The examiner repeated the argument that the claimed subject matter was obvious in view of Reddy. *Id.*, 211-213. First, the examiner stated, in response to the applicant's arguments, that "[t]he familiarity of working with an NK-1 antagonist and its intended use make obvious the administration of netupitant, as claimed,

based on the administration of other NK-1 antagonists, e.g. aprepitant" and thus it "would have been obvious to administer netupitant on day one of five consecutive days." *Id.*, 215. Second, the examiner pointed out to the applicant that its Table 5 from the specification failed "to distinguish over aprepitant, especially since numbers were fairly similar." *Id.*, 215-216. Third, the examiner reiterated that the "binding habit of netupitant is ***an inherent property*** of netupitant" and that the other purported benefits were known in the art. *Id.*, 216. Fourth, the examiner argued that the applicant failed to establish unexpected results, and that "administration of a single dose…may also be construed as ***an inherent property*** of netupitant especially since the prior art teaches administration to patients for treatment of chemotherapy-induced nausea and vomiting." *Id.*, 216-217. The examiner also repeated the non-statutory double patenting rejections. *Id.*, 213-214.

42. In response, the applicant canceled numerous claims and amended then-pending independent claim 16 to recite the "therapeutically effective dose ~~comprises~~ consists of a single dose of netupitant or pharmaceutically acceptable salt thereof administered on day one of said five consecutive days." *Id.*, 324. Similarly, the applicant amended then-pending independent claim 54 to recite "netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days without further administration of netupitant or a pharmaceutically acceptable salt thereof during said five consecutive days." *Id.*,

282-283. The applicant argued that multiple references "suggested that the anti-emetic should be administered during the delayed phase to treat delayed phase emesis, whether the antiemetic was a 5HT3 antagonist, a corticosteroid such as dexamethasone, or an NK1 antagonist." *Id.*, 286. The applicant further argued that Reddy "does not support a prima facie case of obviousness because it fails to explain why a worker of ordinary skill would have administered only one dose of netupitant over a five day period." *Id.*, 287. Finally, the applicant repeated the contention that "Netupitant's efficacy during the acute phase is unexpected." *Id.*, 288-289. The applicant argued that "the 5HT3 pathway mediates emesis during the acute phase, and the NK1 pathway is ***only implicated*** in the delayed phase" so a POSA "would not expect netupitant to be effective during the acute phase." Finally, the applicant again stated it would submit a terminal disclaimer.

43. I again note that in its response, the applicant did not disagree with the examiner's contention that certain claim features of netupitant were inherent. As I summarized above, the examiner had stated that the "binding habit of netupitant is an inherent property of netupitant" and that "administration of a single dose…may also be construed as an inherent property of netupitant especially since the prior art teaches administration to patients for treatment of chemotherapy-induced nausea and vomiting." *Id.*, 216-217.

44. Following the after-final rejection response, the examiner issued an advisory action, stating that the amendments would raise new issues and thus the amendments would not be entered. *Id.*, 312. The applicant then filed a Request for Continued Examination and amended the independent claims to recite "no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said nausea and vomiting for said five consecutive days." *Id.*, 324, 326. The applicant also reiterated that its "position is that it is unexpected that a single dose of netupitant would be effective against nausea and vomiting during the acute and delayed phases of emesis." *Id.*, 328-329.

45. In response to the advisory action and the examiner's repeated characterizations of features as inherent, the applicant did not deny such inherency but instead argued there was no motivation of a person having ordinary skill in the art to administer the NK1 antagonist in the claimed manner. The applicant argued that the inherency "argument also misses the point" because "the examiner bears the burden of proving" a POSA "would have been motivated to administer netupitant only once, when the prior art taught that other NK1 antagonists must be administered 3 times." *Id.*, 329. The applicant argued that "nothing in the prior art would have motivated a worker of ordinary skill in the art to administer netupitant only once during the five-day period." *Id.*

46. Following the Request for Continued Examination and amendments, the examiner filed a new non-final Office action and withdrew from consideration then-pending claims 57-71 because the new claims "are directed to an invention that is independent or distinct from the invention originally claimed." *Id.*, 341-345. The examiner repeated the statutory obvious-type double patenting rejections. *Id.*

47. In response to the non-final Office action, the applicant amended claims to overcome the objection in view of the previous restriction requirement and filed terminal disclaimers over the earlier patents. *Id.*, 350-354. The newly-filed terminal disclaimers used a different form ("PTO/AIA/26") (*id.*, 356-358, 365, 369-371) and were approved (*id.*, 367, 377).

48. The examiner mailed a notice of allowability. *Id.*, 382. The examiner gave no reasons for allowance and withdrew the restriction requirement. *Id.*, 383.

49. The applicant submitted another request for continued examination and submitted an information disclosure statement with several prior art references. *Id.*, 393-519. The examiner again allowed the claims without further substantive examination. *Id.*, 528.

D. US 10,828,297

50. During prosecution of U.S. App. No. 15/923,050, which issued as the '297 patent, I read that the examiner asserted references against the patent applicant. EX1008 (file history of '050 application), 117-123. Specifically, the

examiner stated the claimed invention was obvious over Herrington (EX1016) in view of Reddy (EX1021). The examiner stated that Herrington teaches administration of palonosetron and dexamethasone for prevention of acute and delayed CINV for highly emetogenic chemotherapy but does not teach netupitant. EX1008 (file history of '050 application), 118-119. The examiner stated that Reddy teaches netupitant as a suitable NK-1 antagonist administered in combination with the standard of care for highly emetogenic chemotherapy: a 5-HT_3 receptor antagonist and dexamethasone. *Id.* The examiner concluded an artisan would have reasonably expected success in using netupitant in Herrington's method and that the claims were therefore obvious. *Id.* The examiner also made nonstatutory obviousness-type double patenting rejections in view of claims of the '515 patent, the '975 patent, the '826 patent, and the '357 patent. *Id.*, 121-122.

51. In the Office action, the examiner noted that "the recitation 'wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration' is interpreted as ***a property of netupitant***, and thus ***inherent to patient administration***." *Id.*, 120.

52. In response, the applicant did not amend claims and argued that unexpected results from the combination of palonosetron and netupitant overcame obviousness. *Id.*, 149-153. The applicant indicated a 132 Declaration was submitted with the response to support its arguments but failed to actually submit

the declaration. *Id.*, 152. As with the ’826 patent, the applicant argued that the combination of netupitant and palonosetron provided synergistic inhibition of Substance P; that the combination of netupitant and palonosetron unexpectedly reduced nausea from CINV; and that a single dose of netupitant unexpectedly prevented CINV during the delayed phase. *Id.*, 153-155. The applicant also stated a POSA reasonably could not have predicted the dose of netupitant to combine with palonosetron based on the prior art, and that a POSA would not have reasonably expected netupitant to be independently effective against CINV. *Id.*, 155-156. The applicant also filed a terminal disclaimer to address the obviousness-type double patenting rejection. *Id.*, 156.

53. In its response, the applicant did not disagree with the examiner’s position that netupitant occupying at least 70% of a patient’s striatum NK1 receptors seventy-two hours after administration’ is inherent to patient administration of the netupitant. Instead, with regard to this element, the applicant argued that the specification provided new information without which a POSA would not have arrived at a combination of netupitant and palonosetron. *Id.*, 155 (asserting that “[e]xample 4 of the instant specification, which showed more than 70% of NK1 receptors in the brain were occupied by netupitant 96 hours after a 100 mg dose” supported that, without this information, “a POSA would not have known where even to start with his or her dose ranging studies.”). *Id.*, 155.

54. In a second rejection, the examiner repeated the obviousness arguments, noting that "Applicant refers to a 132 Declaration by Rossi and Pietra, however no such declaration has been submitted. Consequently, applicant's argument is difficult to follow." EX1008 (file history of '050 application), 167. The examiner stated that the prior art showed "it was known at the time of applicants invention that NK-1 receptor antagonists (e.g. netupitant), and palonosetron, specifically, inhibit substance P's ability to cause delayed emesis" and "[t]he fact that applicant has shown that the combination of netupitant and palonosetron effects substance P is not surprising." *Id.*, 168.

55. In response, the applicant submitted an identical copy of the 132 Declaration that had been submitted in the '462 application (which issued as the '826 patent). EX1008 (file history of '050 application), 193-201, 256-264. The applicant made similar arguments in response to the '050 final Office action as were made in the Office action response of the '462 application. *Id.*, 180-188. The applicant argued "[t]he fact that netupitant and palonosetron exhibit synergy at every concentration above the EC50 threshold for substance P proves that the claims are commensurate in scope to the showing of synergy. At all concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined. This showing is necessarily as broad or broader than the 'therapeutically effective' doses recited in the claims." *Id.*, 186.

56. The examiner allowed the application, stating as reason for allowance "applicant discovered that the combination of palonosetron and netupitant provides an unexpected result in regard to treating chemotherapy induced nausea and vomiting. The applicant states, 'One of the most surprising aspects of our research is the synergy observed when netupitant and palonosetron are combined to inhibit substance-P response' (Declaration filed 4/22/20)." EX1008 (file history of '050 application), 2. As I explain in detail below (Sections XXXI, XXXI.C), the applicant's synergy argument for unexpected results was erroneous both because there was no demonstration of superiority as compared to the combination of aprepitant and palonosetron and because the effect of combination treatment was not unexpected.

VI. LEVEL OF SKILL IN THE ART

57. I have been advised by Azurity counsel that "a person having ordinary skill in the art" (POSA) is a hypothetical person to whom one could assign a routine task with reasonable confidence that the task would be successfully carried out. I have been advised further that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

58. The ’826 patent states that “[t]he present invention relates to the use of centrally acting NK_1 antagonists to treat nausea and vomiting, particular[ly] nausea and vomiting induced by highly emetogenic chemotherapy, and to the treatment of such nausea and vomiting over multiple consecutive days. The present invention also relates to combined oral dosage forms of palonosetron and netupitant.” EX1001 (’826 patent), 1:18-24. As I have explained, the patent claims are directed to antiemetic combination therapy. The field of the invention of each of the ’826, ’357, ’297, and ’515 patents is thus related to the administration and pharmacology of antiemetic compounds, especially the combination of NK_1 antagonists in combination with 5-HT_3 antagonists.

59. Based on my specialized education, knowledge, training, and experience, I am familiar with the level of skill of a person having ordinary skill in the art as of the critical date. It is my opinion that a person having ordinary skill in the art of each of the ’826, ’357, ’297, and ’515 patents in November 2009 would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in a field related to pharmacology, biochemistry, medicinal chemistry, oncology, or a related field. It is my opinion that this individual would have worked in consultation with a team including, e.g., a pharmacologist and/or a medicinal chemist familiar with dosing of antiemetic compositions together with a practicing oncologist who diagnoses and treats cancer with antiemetic agents. I was a person having ordinary

skill in the art by this definition before the critical date, and I still am a person having ordinary skill in the art by said definition.

60. A person having ordinary skill in the art also would have had practical knowledge and experience about metabolism studies, in-vitro and in-vivo testing, formulation, and combination therapy. A person having ordinary skill would have been familiar with prior art pertaining to the above, including the patents and publications discussed herein.

VII. SUMMARY OF OPINIONS

61. It is my opinion that each claim of the ’826, ’357, ’515, and ’297 patents was obvious in view of prior art references. Further, it is my opinion that there are not sufficient secondary considerations such as unexpected results to overcome the obviousness shown by the prior art.

62. I have evaluated whether the combination of prior art references MASCC and Hoffmann discloses the claimed features of the ’826 patent. As I explain further below, it is my opinion that the combination of MASCC and Hoffmann discloses each and every element of claims 19, 22-23 and 25 of the ’826 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 19, 22-23 and 25 of the ’826 patent as a whole with a

reasonable expectation of success. I explain my opinion further below in Section XI (’826 patent, Ground 1).

63. I have evaluated whether the combination of prior art references MASCC and Bös discloses the claimed features of the ’826 patent. As I explain further below, it is my opinion that the combination of MASCC and Bös discloses each and every element of claims 19-20, 22-23 and 25 of the ’826 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 19-20, 22-23 and 25 of the ’826 patent as a whole with a reasonable expectation of success. I explain my opinion further below in Section XII (’826 patent, Ground 2).

64. I have evaluated whether the combination of prior art references MASCC, Bös, and Aloxi discloses the claimed features of the ’826 patent. As I explain further below, it is my opinion that the combination of MASCC, Bös, and Aloxi discloses each and every element of claims 19-23 and 25 of the ’826 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 19-23 and 25 of the ’826 patent as a whole with a reasonable expectation of success. I explain my opinion further below in Section XIII (’826 patent, Ground 3).

65. I have similarly evaluated whether the combination of prior art references Herrstedt, Hoffmann, and Hargreaves discloses the claimed features of the ’826 patent. As further explained below, it is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves discloses each and every element of claims 1-3, 8-10, 15-18 and 24 of the ’826 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 1-3, 8-10, 15-18 and 24 of the ’826 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XIV (’826 patent, Ground 4).

66. I have similarly evaluated whether the combination of prior art references Herrstedt, Bös, and Hargreaves discloses the claimed features of the ’826 patent. Further explained below, it is my opinion that the combination of Herrstedt, Bös, and Hargreaves discloses each and every element of claims 1-3, 6-10, 15-18 and 24 of the ’826 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 1-3, 6-10, 15-18 and 24 of the ’826 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XIV (’826 patent, Ground 5).

67. As I explain in Section XVI below (’826 patent, Ground 6), dependent claims 4 and 5 were obvious based on the combination of Herrstedt, Bös, Hargreaves and optionally Herrington. As I explain in Section XVII below (’826 patent, Ground 7), dependent claims 10-14 were obvious based on the combination of Herrstedt, Bös, Hargreaves and optionally Aloxi.

68. I have similarly evaluated whether the combination of prior art references Herrstedt, Bös, and optionally Herrington discloses the claimed features of the ’515 patent. Further explained below, it is my opinion that the combination of Herrstedt, Bös, and optionally Herrington discloses each and every element of claims 11-17 and 19-23 of the ’515 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 11-17 and 19-23 of the ’515 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XVIII (’515 patent, Ground 1).

69. I have similarly evaluated whether the combination of prior art references Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the claimed features of the ’515 patent. Further explained below, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses each and every element of claims 1-10 and 18 of the ’515 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would

have had good reason to combine these references in a manner that satisfies each of claims 1-10 and 18 of the ’515 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XIX (’515 patent, Ground 2).

70. I have also evaluated whether the combination of prior art references Herrstedt and Bös discloses the claimed features of the ’297 patent. Further explained below, it is my opinion that the combination of Herrstedt and Bös discloses each and every element of claims 1-4, 8-13, 17-19, and 23 of the ’297 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 1-4, 8-13, 17-19, and 23 of the ’297 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XX (’297 patent, Ground 1).

71. As I explain in Section XXI below (’297 patent, Ground 2), dependent claims 5-6, 14-15, and 20-21 were obvious based on the combination of Herrstedt, Bös, Aloxi. As I explain in Section XXII below (’297 patent, Ground 3), dependent claims 7, 16, and 22 were obvious based on the combination of Herrstedt, Bös, and Hargreaves.

72. I have also evaluated whether the combination of prior art references Herrstedt and Bös discloses the claimed features of the ’357 patent. Further

explained below, it is my opinion that the combination of Herrstedt and Bös discloses each and every element of claims 1-17, 40, 52-54, and 56-62 of the ’357 patent. It is also my opinion that a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each of claims 1-17, 40, 52-54, and 56-62 of the ’357 patent as a whole with a reasonable expectation of success. My opinion is elaborated further below in Section XXIII (’357 patent, Ground 1).

73. As I explain in Section XXIV below (’357 patent, Ground 2), dependent claims 18-19, 25-27, 30-32, and 41-42 were obvious based on the combination of Herrstedt, Bös, and optionally Herrington. As I explain in Section XXV below (’357 patent, Ground 3), dependent claim 20 was obvious based on the combination of Herrstedt, Bös, optionally Herrington, and optionally Aloxi. As I explain in Section XXVI below (’357 patent, Ground 4), dependent claim 55 was obvious based on the combination of Herrstedt, Bös, and Hargreaves. As I explain in Section XXVII below (’357 patent, Ground 5), dependent claims 24 and 29 were obvious based on the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. As I explain in Section XXVIII below (’357 patent, Ground 6), dependent claim 28 was obvious based on the combination of Herrstedt, Bös, Bonadeo, and optionally Herrington. As I explain in Section XXIX below (’357 patent, Ground 7), dependent claims 21-23, 33-35, 37-39, 43-44, and 46-51 were

obvious based on the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. As I explain in Section XXX below ('357 patent, Ground 8), dependent claims 36 and 45 were obvious based on the combination of Herrstedt, Bös, Bonadeo, Hargreaves, optionally Herrington, and optionally Aloxi.

VIII. TECHNICAL BACKGROUND

74. Therapeutic combinations of an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and dexamethasone for treating chemotherapy-induced nausea and vomiting (CINV) was very well established prior to the critical date. Administering the combination of antiemetics prophylactically (i.e., prior to administration of the chemotherapy) provided relief from nausea and vomiting associated with the emetogenic chemotherapy. Multiple combinations of assorted NK_1 receptor antagonists and 5-HT_3 receptor antagonists with dexamethasone had proven to be effective at treating CINV in patients, thus improving comfort for patients undergoing chemotherapy. It was known that palonosetron was a new 5-HT_3 receptor antagonist that had significantly increased half-life, and it was known that netupitant was a new NK_1 receptor antagonist with high affinity and selectivity for the NK_1 receptor. It was also known in the field that when one administered an NK_1 receptor antagonist with dexamethasone, the amount of dexamethasone administered should be reduced in order to address metabolic interactions. Each of these aspects is referenced throughout the prior art, and I provide additional

disclosure throughout the below sections. Below is a chart that provides a high level summary of relevant disclosures from some of the prior art references discussed in the sections below.

Disclosed element	**Reference(s)**
Combination therapy: NK_1 receptor antagonist, 5-HT_3 receptor antagonist, dexamethasone	MASCC (EX1013), Herrstedt (EX1010), Poli-Bigelli (EX1039), Hesketh (EX1037)
The combination is effective for treating highly emetogenic chemotherapy or moderately emetogenic chemotherapy	MASCC (EX1013), Herrstedt (EX1010), Poli-Bigelli (EX1039), Hesketh (EX1037)
The combination is prophylactically administered (i.e., prior to chemotherapy)	MASCC (EX1013), Poli-Bigelli (EX1039), Hesketh (EX1037)
Palonosetron as a new 5-HT_3 receptor antagonist	MASCC (EX1013), Herrstedt (EX1010), Aloxi (EX1015)
Netupitant as a new NK_1 receptor antagonist	Hoffmann (EX1011), Bös (EX1014)

Netupitant is administered in a therapeutically effective dose (e.g., 300 mg netupitant)	Bös (EX1014)
NK_1 receptor antagonist occupies NK_1 receptors in striatum of a patient's brain	Hargreaves (EX1012)
A single dose of NK_1 receptor antagonist administered on day one of the five-day treatment period, no additional administrations	Herrington (EX1016)

75. Chemotherapy is a common treatment for cancer but unfortunately may cause side effects including nausea and vomiting. EX1013 (MASCC), 20 ("vomiting and nausea continue to be significant side effects of cancer therapy"); EX1010 (Herrstedt), Abstract ("Nausea and vomiting are ranked as the most severe side effects to chemotherapy by cancer patients."); EX1021 (Reddy), Abstract ("Despite significant advances in supportive care in oncology, many patients with cancer still experience chemotherapy-induced nausea and vomiting (CINV)."). Many common chemotherapeutic agents, such as cisplatin, are classified as highly emetic. EX1013 (MASCC), Table 1; EX1010 (Herrstedt), 146; EX1016

(Herrington), 2086. This is due in part to the release of Substance P and serotonin, which trigger a vomiting reflex. EX1043 (Saito), Abstract ("This review attempts to bring together some of the evidence suggesting the roles of substance P and its receptor, neurokinin NK1 receptor, in the brainstem nuclei in the development of emesis."); *id.*, 87 ("Serotonin and Substance P are released from the enterochromaffin cells of the stomach and intestine (gastrointestinal tract) and from sensory neurons, respectively, by radiation and emetic agents such as copper sulfate or anticancer drugs"). Similar to chemotherapy-induced nausea and vomiting (CINV), radiotherapy-induced nausea and vomiting (RINV) and post-operative nausea and vomiting (PONV) are instigated by overlapping triggers. EX1043 (Saito), 89-90 ("Serotonin and Substance P are released from the enterochromaffin cells of the stomach and intestine (gastrointestinal tract) and from sensory neurons, respectively, by radiation and emetic agents such as copper sulfate or anticancer drugs."); EX1021 (Reddy), 141 ("Casopitant (GW679769) is a NK-1 antagonist currently being developed to prevent CINV and postoperative nausea and vomiting in patients with cancer."). Antiemetic therapeutics have been developed to block this reflex and provide relief to patients. EX1013 (MASCC), 22 ("Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory

peptide Substance P."); *see also* EX1010 (Herrstedt), Table 2; EX1043 (Saito), 87-89.

76. Substance P is a type of neuropeptide, specifically a tachykinin. EX1043 (Saito), 90; EX1014 (Bös), 1:6-12; EX1023 (Campos), 1760. Neuropeptides are small peptides used by neurons to communicate with each other. EX1043 (Saito), 90; EX1014 (Bös), 1:6-12; EX1023 (Campos), 1760. Those in the field understood Substance P, in particular, to play a role in many biological processes, such as the regulation of mood disorders, anxiety, stress, as well as nausea, vomiting, and pain. EX1011 (Hoffmann), 1362; EX1012 (Hargreaves), 23; EX1014 (Bös), 1:23-67, 39:42-48; EX1043 (Saito), Abstract; EX1023 (Campos), 1760. It has been known for decades that substance P activity in the brain induces emesis:

> Substance P is one of four mammalian tachykinnins found in neurons (including vagal afferent fibers) innervating the brainstem nucleus tractus solitarii and the area postrema. Both regions are intimately involved in the induction of vomiting. Exogenous Substance P applied to cells in the nucleus tractus solitarii results in emesis.

EX1023 (Campos), 1760.

77. When chemotherapeutic agents are administered, they can stimulate the release of Substance P in some patients. EX1043 (Saito), 87, 90-91. This neuropeptide, in turn, binds to a specific receptor known as the neurokinin 1 (NK_1)

receptor. *Id.*; EX1023 (Campos), 1760. The activation of NK_1 triggers feelings of nausea and a vomiting reflex. EX1012 (Hargreaves), Abstract; EX1011 (Hoffmann), 1362; EX1023 (Campos), 1760. To counteract this, drugs that block the NK_1 receptor, known as NK_1 receptor antagonists, have been developed. EX1014 (Bös), 2:1-65; EX1011 (Hoffmann), Abstract; EX1023 (Campos), Abstract. These drugs, such as aprepitant and fosaprepitant (prodrug of aprepitant), prevent Substance P from binding to the NK_1 receptors, thereby blocking the activation of the vomiting reflex and preventing the associated nausea and vomiting. EX1011 (Hoffmann), Abstract, 1362; EX1021 (Reddy), Abstract; EX1023 (Campos), Abstract (MK-869 is aprepitant). I refer to the NK_1 receptor antagonists aprepitant as a first generation NK_1 receptor antagonist. Prior to the critical date, second generation NK1 receptor antagonists were known (e.g., fosaprepitant, and casopitant) and in particular one second generation NK_1 receptor antagonist—netupitant—was known to have high selectivity and affinity for the NK_1 receptor, excellent oral activity, and excellent penetration into the central nervous system (CNS). EX1011 (Hoffmann), 1364; EX1014 (Bös), 18:42-48. Netupitant had also shown success as an NK1 receptor antagonist in vivo and was known to have a long half-life. EX1014 (Bös), 18:64-19:25, 19:31-37. Thus netupitant—a second generation NK_1 receptor antagonist—had favorable characteristics. Additionally, netupitant acted in the same mechanistic pathway

(i.e., antagonism of the NK_1 receptor) as other NK_1 receptor antagonists to achieve the same therapeutic goal (e.g., treatment of CINV).

78. It was known in the field prior to the critical date to apply routine dose-ranging studies to identify effective therapeutic doses of active pharmaceutical ingredients including NK_1 receptor antagonists, such as netupitant. For example, Bös provides a clear starting point for dose-range studies (10 to 1,000 mg) (EX1014 (Bös), 42:5-11), and it would have been routine for skilled artisans to test doses within the recited range—including those within the center order of magnitude (i.e., 100 mg band), and near the center of that range, including e.g. 300 mg and 450 mg—to identify the therapeutically effective amount to administer to patients receiving chemotherapy, thus treating chemotherapy-induced nausea and vomiting. The ’826 patent confirms the routine nature of such dose-ranging studies. EX1001 (’826 patent), 16:37-60 (Example 4) (dose escalation studies of netupitant including 100 mg, 300 mg, and 450 mg administrations); *id.*, 16:62-19:43 (Example 5) (dose response studies of netupitant including 100 mg, 200 mg, and 300 mg administrations). The skilled artisan thus would have understood from the prior art that administration of a therapeutically effective amount of netupitant (e.g., about 300 mg) was obvious.

79. Another substance involved in chemotherapy-induced nausea and vomiting is serotonin, also known as 5-hydroxytryptamine or 5-HT. EX1010

(Herrstedt), Abstract; EX1043 (Saito), 89-90. Similar to Substance P, serotonin also is released in response to certain chemotherapeutic agents or radiation treatments. EX1043 (Saito), 89-90. It is primarily released by cells in the small intestine. EX1027 (De Leon), 413. When released, serotonin can bind to a specific receptor known as the 5-HT_3 receptor, which can also trigger a vomiting reflex. EX1010 (Herrstedt), Abstract; EX1043 (Saito), 89-90. Drugs that block the 5-HT_3 receptor, known as 5-HT_3 receptor antagonists, have been developed to prevent this emetic effect. EX1027 (De Leon), Abstract; EX1043 (Saito), 89-90. These drugs, which include ondansetron, granisetron, and palonosetron, prevent serotonin from binding to the 5-HT_3 receptor, thus preventing the downstream vomiting reflex. EX1027 (De Leon), Abstract; EX1043 (Saito), 89-90.

80. Palonosetron, in particular, showed improved efficacy as compared to other 5-HT_3 receptor antagonists and could be administered as a single dose, which the art suggested was a result of its long half-life (~40 hours) vs ondansetron (~3-6 hours):

> Single-dose palonosetron was as effective as ondansetron in preventing acute CINV following HEC, and with dexamethasone pre-treatment, its effectiveness was significantly increased over ondansetron throughout the 5-day post-chemotherapy period.

EX1022 (Aapro), 1441; EX1017 (Bonadeo), 1 (“a highly efficacious anti-nauseant ant anti-emetic for use with emetogenic anti-cancer chemotherapies”); *id.* (“high

affinity as an antagonist for the 5-hydroxyltryptamine 3 receptor precursor (5-HT_3 receptor), and showing low affinity for other receptors such as dopamine receptors"); *id.* ("a potent and selective antagonist"). Single dose administration of therapeutic agents was known to be beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient single-day three-drug antiemetic regimen…."). The art recognized that both 0.25 mg and 0.75 doses of palonosetron were effective for antiemesis. *See, e.g.*, EX1022 (Aapro), 1447 ("In this trial the approved 0.25-mg dose of palonosetron was as effective as the 0.75-mg dose for prevention of CINV."); EX1027 (De Leon), 414 ("Compared with ondansetron 32 mg, palonosetron 0.25 mg achieved significantly higher CR [complete response] rates" and "Palonosetron 0.75 mg did not demonstrate a statistically significant advantage in efficacy compared with palonosetron 0.25 mg.").

81. 5-HT_3 receptor antagonists are particularly effective at preventing acute nausea and vomiting that occurs on the day of chemotherapy. EX1043 (Saito), 89, 91. However, for optimal control of delayed nausea and vomiting that can occur several days after chemotherapy, they are often combined with other drugs, such as dexamethasone and NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract; EX1013 (MASCC), 22-23. NK_1 receptor antagonists, such as aprepitant,

can further improve the prevention of acute nausea and vomiting on the day of chemotherapy. EX1023 (Campos), 1763 & Fig. 2.

82. Dexamethasone is a type of corticosteroid medication that has potent anti-inflammatory effects. EX1010 (Herrstedt), 144-145. While its exact mechanism of action in preventing nausea and vomiting is not fully understood, it is nonetheless a well-known antiemetic and its prevention of emetic effects is thought to involve several actions. *Id.* Prior to the critical date, it was known in the field that dexamethasone administered in combination with an NK_1 receptor antagonist (such as aprepitant) was administered to the patient on day one in a dose which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said NK_1 receptor antagonist (i.e., in a dose less than 20 mg). *See, e.g.*, Sections IX.A, IX.E, below. The shared specification of the challenged patents identifies 20 mg as the minimum effective dose of dexamethasone when administered alone. *See, e.g.*, Section XI.B; EX1001 (’826 patent), 7:62-8:4 (citing Jordan, EX1019). Jordan shows that when dexamethasone is administered with NK_1 receptor antagonist (aprepitant), it is administered in a 12 mg dose, which is 60% of the minimum effective dose when administered alone (20 mg x 0.6 = 12 mg).

Table 3. Recommended doses of antiemetics [4–6]

Agent	Route	Recommended dose (once daily)
5-HT_3-receptor antagonist		
Ondansetron	Oral	24 mg (high), 16 mg (moderate)[a]
	i.v.	8 mg (0.15 mg/kg)
Granisetron	Oral	2 mg
	i.v.	1 mg (0.01 mg/kg)
Tropisetron	Oral	5 mg
	i.v.	5 mg
Dolasetron	Oral	100 mg
	i.v.	100 mg (1.8 mg/kg)
Palonosetron	i.v.	0.25 mg
Steroids		
Dexamethasone	Oral/i.v.	12 mg (highly emetogenic, with aprepitant), 20 mg without aprepitant; 8 mg (moderately emetogenic); 8 mg (high/moderate) days 2 and 3
NK_1-receptor antagonist		
Aprepitant	Oral	125 mg on day 1, 80 mg on days 2 and 3

[a]8 mg twice daily is recommended.

EX1019 (Jordan), Table 3 (highlighting added). The field taught it was necessary to reduce corticosteroids when administered with an NK_1 receptor antagonist to minimize side effects associated with high levels of dexamethasone due to inhibition of dexamethasone metabolism and corresponding increase of exposure. *E.g.*, Sections IX.A, IX.E, XI.B, below. For example, it was known that corticosteroids such as dexamethasone had "been associated with increased susceptibility to infection when administered in high doses." EX1025 (Chawla), 2299; *id.* ("increases in infection were noted that were assumed to be due to elevated dexamethasone levels as a result of the pharmacokinetic interaction" when a 20 mg dose of dexamethasone was administered with 125 mg aprepitant).

83. It was also known in the field to administer dexamethasone on days subsequent to the day of chemotherapy (i.e., subsequent to "Day 1") as well as

prophylactically prior to chemotherapy. Subsequent administrations of dexamethasone were routine to improve delayed antiemetic efficacy. EX1010 (Herrstedt), 146; EX1039 (Poli-Bigelli), Abstract; EX1037 (Hesketh), Abstract; *see also, e.g.*, EX1024 (Chang), 1480 ("For delayed emesis…a 5-HT3 receptor antagonist with dexamethasone is recommended."). Such administrations of dexamethasone on subsequent days is shown, for example, by the National Comprehensive Cancer Network antiemetic guidelines.

TABLE 83.7. Summary of National Comprehensive Cancer Network (NCCN) antiemetic guidelines.

1. **Highly emetogenic chemotherapy (level 5)**
   - Aprepitant (NK-1 antagonist) pre- and postchemotherapy **AND**
   - Dexamethasone pre- and postchemotherapy **AND**
   - 5-HT3 inhibitor pre- and postchemotherapy
   - ± Benzodiazepine if needed
2. **Moderately emetogenic chemotherapy (level 3–4)**
   Day 1
   - Dexamethasone **AND**
   - 5-HT3 inhibitor **OR**
   - 5-HT3 inhibitor
   - ± Benzodiazepine if needed
   - ± Aprepitant if needed

   Days 2–4
   - Dexamethasone **OR**
   - 5-HT3 inhibitor pre- and postchemotherapy **OR**
   - Metoclopramide ± diphenhydramine **OR**
   - Aprepitant **AND** dexamethasone
   - ± Benzodiazepine if needed
3. **Low emetogenic potential chemotherapy (level 2)**
   a. Dexamethasone prechemotherapy **OR**
   b. Phenothiazine as needed **OR**
   c. Metoclopramide + diphenhydramine as needed
   d. ± Benzodiazepine as needed
4. **Minimal emetogenic potential chemotherapy (level 1)**
   a. No prechemotherapy emesis prevention
   b. Use phenothiazines/metoclopramide/benzodiazepines as needed

Source: NCNN Antiemesis Practice Guidelines in Oncology. Version 1.2004, 03-30-04. National Comprehensive Cancer Network; 2004. Available at http//www.nccn.org. Accessed April 10, 2004.

EX1024 (Chang), 1480; *see also, e.g.*, EX1025 (Chawla), 2292 ("Every morning between 8 AM and 10 AM on Days 2-5, patients took a capsule formulation of

either aprepitant or placebo. In addition, all patients received oral dexamethasone 8 mg."); EX1016 (Herrington), 2081 ("On Day 1, Arms A and B received a single dose of palonosetron 0.25 mg intravenously and dexamethasone 12 mg orally before receiving highly emetogenic chemotherapy…. All patients in the 3 study arms received dexamethasone 8 mg orally daily on Days 2-4….").

84. It was common before 2009 to manage chemotherapy-induced nausea and vomiting by administering a combination of drugs in these classes (i.e., an NK_1 receptor antagonist, a 5-HT_3 receptor antagonist, and a corticosteroid), targeting different aspects of the vomiting reflex to provide the most comprehensive relief to patients. EX1011 (Hoffmann), Abstract; EX1013 (MASCC), 22, 25. It was also known in the field that the addition of an NK_1 receptor antagonist to a combination therapy of 5-HT_3 receptor antagonist and dexamethasone would improve the therapeutic effect. *Id.*; *see also* EX1010 (Herrstedt), 146. Indeed, the '826 patent confirms this, showing that "[a]ll doses of netupitant were statistically superior to palonosetron alone" including its 100 mg, 200 mg, and 300 mg doses of the NK_1 receptor antagonist, netupitant. EX1001 ('826 patent), 18:25-33 & Table 5. The '826 patent shows at best marginal improvement in treating chemotherapy-induced nausea and vomiting between the 100 mg netupitant dose and the 300 mg netupitant dose. *Id.*, Table 5, Table 6 (reproduced below).

TABLE 5

COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)
CR, Overall Phase, 0-120 h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, 0-24 h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120 h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

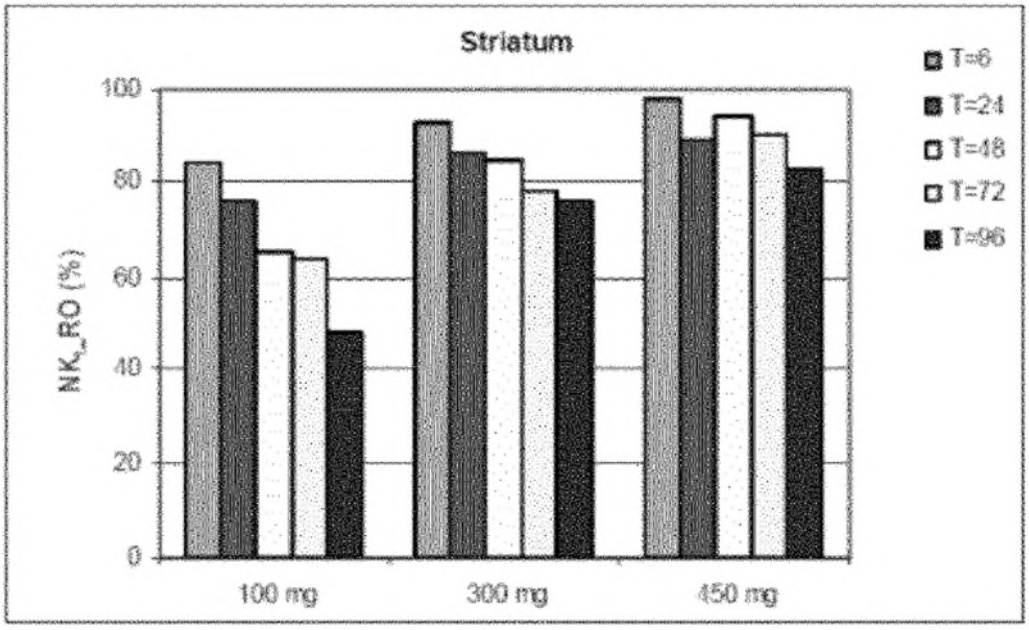
*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

85. Those in the field understood that each of the NK_1 receptor antagonist, the 5-HT_3 receptor antagonist, and the corticosteroid were administered prophylactically (i.e., prior to chemotherapy) to provide therapeutic effect. *See, e.g.*, EX1039 (Poli-Bigelli), 3092 ("One hour prior to cisplatin, patients received either aprepitant or placebo. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone."); EX1037 (Hesketh), 4113 ("One hour before cisplatin, patients received either aprepitant or placebo. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone"). When a therapeutic amount of NK_1 receptor antagonist is prophylactically administered, it enters into systemic circulation and provides a corresponding increase of blood levels of the therapeutic agent. From the circulatory system, the NK_1 receptor antagonist crosses the blood-brain barrier and provides corresponding occupancy of NK_1 receptors in the brain striatum. EX1012 (Hargreaves), 22-23. It was known in the field that therapeutically effective administrations of NK_1 receptor antagonists naturally resulted in occupancy of over 75% (and up to 90%) of NK_1 receptors in the striatum. EX1012 (Hargreaves), 23 ("high levels of NK_1 receptor occupancy were associated with significant antidepressant effects and optimal activity against CINV. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked $\geq$ 90% of NK_1 receptors in the CNS (Figure 6B),

whereas the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B).”). Skilled artisans in the field thus understood that such occupancy of NK_1 receptors in the striatum corresponded with administration (e.g., prophylactic administration) of a therapeutically effective dose of an NK_1 receptor antagonist, which would treat nausea and vomiting induced by chemotherapy.

86. As I explained above, the art rendered obvious the therapeutically effective dose of netupitant (e.g., 300 mg) and the art disclosed netupitant’s long half life. In view of Hargreaves, persons of skill in the art would have reasonably expected that prophylactic administrations of therapeutically effective amounts of an NK_1 receptor antagonist (e.g., 300 mg netupitant), which had a long half life (EX1014 (Bös), 18:64-19:25, 19:31-37) would naturally result in continued high occupancy of the striatum NK_1 receptors that continued at 72 hours, as well as at 96 hours. The ’826 patent confirms that the expected therapeutically effective doses of netupitant (e.g., 300 mg, 450 mg) occupy NK_1 receptors in the striatum, and that for any sufficiently large dose of netupitant, the natural result of administering such obvious doses is NK1 receptor antagonism greater than 70% after 72 (and after 96) hours. *See*, *e.g.*, EX1001 (’826 patent), Figure 5:



The ’826 patent reports that this natural result is achieved in 100% of patients that received a dose of netupitant 300 mg or larger. *Id.*, 16:37-60.

IX. ANALYSIS OF ASSERTED REFERENCES

A. MASCC

87. The Multinational Association of Supportive Care in Cancer (“MASCC”) (EX1013) is an international and interdisciplinary organization that is dedicated to researching and supporting care in cancer. MASCC periodically publishes recommendations for antiemetic therapies for practitioners, providing updates to the standard of care by applying relevant and recent research. EX1013 (MASCC), 20.

88. In 2006, the Antiemetic Subcommittee of MASCC published an update “on antiemetic regimens to prevent emesis induced by high, moderate, low

and minimal risk chemotherapy." The update was published in the journal ANNALS OF ONCOLOGY in January of 2006. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

89. MASCC described NK_1 receptor antagonists improved the previous standard therapy of a 5-HT_3 receptor antagonist with dexamethasone. It explained that the standard antiemetic treatment had been:

> a 5-HT3-receptor antagonist plus dexamethasone as the regimen of choice for the prevention of acute emesis in cisplatin-treated patients. However, aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK_1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT3-receptor antagonist plus dexamethasone[].

EX1013 (MASCC), 22. MASCC further reported that dexamethasone dose was reduced when given in combination with aprepitant due to prior pharmacokinetic studies that had found aprepitant approximately doubled dexamethasone levels. *Id.* The triple therapy was superior to the standard dual combination therapy of 5-HT_3 antagonist with dexamethasone, as observed by applying a "primary endpoint [of] complete response (no emesis, no use of rescue antiemetics) over the 5-day study period." *Id.*

90. The Anti-emetic Subcommittee of MASCC thus recommended a three-drug antiemetic drug combination using (1) a 5-HT_3 receptor antagonist; (2) the NK_1 receptor antagonist aprepitant; and (3) dexamethasone as the standard of care to prevent acute vomiting and nausea:

> [T]o prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).

EX1013 (MASCC), 22. Likewise, for delayed emesis induced by highly emetogenic chemotherapy:

> the panel recommended that given the dependence of delayed emesis and nausea on acute antiemetic outcome, optimal acute antiemetic prophylaxis should be employed. For cisplatin, this includes a three-drug combination of aprepitant, a 5-HT3-receptor antagonist and dexamethasone.

Id. at 23. This recommendation had been given despite comparative studies with the then-existing standard treatment. *Id.* Furthermore, the MASCC publication disclosed both oral and intravenous administration of 5-HT_3 antagonists and dexamethasone, as well as the oral administration of the NK_1 receptor antagonist. *Id.* at 23-24.

91. The MASCC report also clarified that palonosetron was the better option among 5-HT_3 antagonists:

> Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists. Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases[.]

Id. at 24. The report also recommended the use of palonosetron with highly emetic-risk chemotherapy. *Id.* at Table 3.

B. Hoffmann

92. Hoffmann (EX1011) is an article that published in the scientific journal, BIOORGANIC & MEDICINAL CHEMISTRY LETTERS in 2005. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

93. Hoffmann discloses a class of potent and orally active neurokinin-1 (NK_1) receptor antagonists for therapeutic use to control nausea and vomiting caused by cancer chemotherapy, as well as treat mood disorders like anxiety and depression. EX1011 (Hoffmann), Abstract. Hoffmann explains:

> [R]ecent clinical trials have demonstrated an important therapeutic application for NK_1 receptor antagonists in the control of cancer

> chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression. MK-869 (aprepitant) was the first NK_1 receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.

EX1011 (Hoffmann), 1362 (endnote omitted).

94. Hoffmann further identifies netupitant as a member of the same NK_1 antagonist class as aprepitant, specifically noting netupitant's favorable characteristics including high affinity and excellent oral activity. *Id.*, 1364. Hoffmann also identified that netupitant had excellent penetration into the central nervous system, and it was understood in the field that "[t]he SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli," and "local application of SP" related to emesis. EX1011 (Hoffmann), 1364; EX1012 (Hargreaves), 18. Hoffmann explains moieties of interest (including netupitant) were tested in vivo and were shown to potently inhibit NK_1 agonist-induced foot tapping behavior in gerbils after oral administration. EX1011 (Hoffmann), 1365.

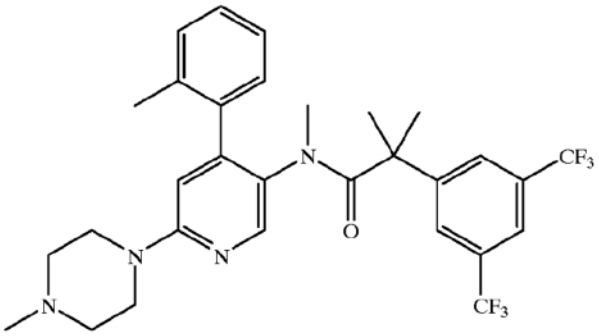
C. Bös

95. U.S. Patent number 6,297,375 to Bös et al. ("Bös") (EX1014) issued on October 2, 2001. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

96. Bös describes the application of NK_1 receptor antagonists to inhibit Substance P interactions associated with numerous conditions including chemotherapy-induced emesis. Bös describes the use of NK_1 receptor antagonists for "mediation of the emetic reflex and the modulation of central nervous system (CNS) disorders[.]" EX1014 (Bös), 1:15-56. Bös teaches that "neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting" such as in "the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist." *Id.*, 1:59-67.

97. Bös discloses netupitant as belonging to a class of NK_1 receptor antagonists. Bös discloses its class of compounds are useful as NK_1 receptor antagonists (EX1014 (Bös), 2:1-65) and explicitly identifies netupitant ("formula Ib"), which is "characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)[.]" (*id.*, 14:32-38). Bös provides the chemical structure of netupitant:

Ib



Id., 14:9-30. Bös also provides a method for synthesizing netupitant. *Id.*, 14:40-18:30.

98. Bös conducted in vitro studies that showed netupitant "is ***a potent and selective antagonist*** at recombinant human neurokinin, (NK_1) receptors expressed in CHO cells. It ***has an affinity (pKi) of 9.0*** for the human NK_1 receptor and over 2 orders of magnitude of selectivity for the NK_1 receptor compared to NK_2 and NK_3 receptors and compared to over 50 other binding sites that have been evaluated." EX1014 (Bös), 18:42-48. Bös states that "[a] pKi in the range of about 8.0 to about 9.8 indicates an ***especially high affinity***," and thus clarifies that netupitant has an especially high affinity for NK_1 receptors.

99. Bös discloses numerous in vivo studies showing efficacy of netupitant. Bös describes studies in gerbils (EX1014 (Bös), 18:64-19:9), ferrets (19:10-20), and Suncus murinus (commonly known as the Asian house shrew) (19:21-25). For example, Bös administered to ferrets an oral dose of netupitant to evaluate the antiemetic effect with induction by chemical agents, including the

highly emetogenic chemotherapeutic agent cisplatin. *Id.*, 19:10-20. By administering netupitant to the subject before exposure to the emetogenic agent, netupitant "completely blocked the emesis induced by the emetogens." *Id.*

100. Bös identified netupitant as having a long half-life. Bös explains that in rats, the terminal half-life was 24 hours, while "[i]n dogs the molecule had a half-life of 18 hours[.]" *Id.*, 19:31-37. In gerbils, netupitant had a "functional half life of 30 hours." *Id.*, 18:64-19:10.

101. Bös also discloses a dose range for the therapeutically effective amount of its NK_1 receptor antagonists, which includes netupitant. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration ***a daily dosage of about 10 to 1000 mg per person*** of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

D. Aloxi

102. ALOXI (palonosetron HCl) Capsules ("Aloxi") (EX1015) is a drug label that was approved by the FDA in August 2008. EX1015 (Aloxi), 1, 6. I understand it is prior art that was publicly available before the earliest possible priority date of November 18, 2009. I also understand EX1015 was obtained

directly from the FDA website (EX1058) by selecting the label corresponding to the approval date of August 22, 2008.

103. Aloxi discloses the use of palonosetron hydrochloride ("palonosetron HCl") as a potent and selective 5-HT_3 receptor antagonist indicated for "[m]oderately emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses." EX1015 (Aloxi), 1; *id.*, 3 ("Palonosetron is a 5-HT3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors."). Aloxi also suggests use of palonosetron for treating both moderately and highly emetogenic chemotherapy, such as cisplatin. *Id.*, 1 (indicated for moderately emetogenic chemotherapy), 3 ("Palonosetron as a 5-HT_3 receptor antagonist with a strong binding affinity for this receptor and little or no affinity for other receptors. Cancer chemotherapy may be associated with a high incidence of nausea and vomiting, particularly when certain agents, ***such as cisplatin***, are used."). Because Aloxi describes palonosetron as binding 5-HT_3 receptors with strong affinity and the applicability of antagonizing those receptors for preventing nausea and vomiting following administration of cisplatin, a POSA would have understood Aloxi to suggest the use of palonosetron for preventing CINV associated with highly and moderately emetogenic chemotherapy.

104. Aloxi teaches its dose is an orally administered capsule that contains 0.56 mg palonosetron HCl, corresponding to 0.5 mg of the free base of palonosetron. Aloxi also describes its dose form as a 0.5 mg capsule. EX1015 (Aloxi), 1 ("one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy"), *id.*, 1 ("0.5 mg capsule"), 2 (similar). The reference details that the capsule was dosed orally. *Id.*, 3 ("Following oral administration, palonosetron is well absorbed with its absolute bioavailability reaching 97%.... In 36 healthy male and female subjects given a single oral dose of ALOXI Capsules 0.5 mg,…. In 12 cancer patients given a single oral dose of palonosetron 0.5 mg one hour prior to chemotherapy…."), 2 ("In clinical trials for the prevention of nausea and vomiting induced by moderately emetogenic chemotherapy…patients received oral palonosetron in doses ranging from 0.25 mg to 0.75 mg."), 4 (clinical studies including 0.5 mg oral ALOXI capsules given one hour prior to chemotherapy). The Aloxi capsules each contain 0.56 mg palonosetron HCl corresponding to 0.5 mg of palonosetron free base *Id.*, 3 ("Each light beige opaque soft gelatin ALOXI Capsule contains ***0.56 mg of palonosetron HCl*** equivalent to palonosetron 0.5 mg."), 4 ("ALOXI Capsules, 0.5 mg (free base) are supplied as light beige opaque soft gelatin capsules…").

105. Aloxi instructs the palonosetron HCl capsules are to be administered one hour prior to chemotherapy. EX1015 (Aloxi), 5 ("Take one ALOXI Capsule

by mouth about one hour before you get your anti-cancer medicine (chemotherapy)."); *id.*, 1 ("Adult Dosage: one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy[.]"). Aloxi also teaches that the palonosetron HCl capsules can be administered with chemotherapeutic agents, systemic corticosteroids (e.g., dexamethasone), and with other antiemetic and antinausea agents. *Id.*, 2 ("In controlled clinical trials, ALOXI Capsules have been safely administered with chemotherapeutic agents, systemic corticosteroids, analgesics, and drugs for gastrointestinal disorders including function gastrointestinal disorders, acid-related disorders, and antiemetics/antinauseants.").

106. Aloxi's orally administered capsules of palonosetron HCl have substantively similar efficacy to intravenously administered palonosetron. Aloxi describes a comparison of its 0.5 mg oral capsules to 0.25 intravenous palonosetron, wherein the results showed similar efficacy. EX1015 (Aloxi), 4 ("As shown in Table 3, ALOXI Capsules 0.5 mg demonstrated non-inferiority to the active comparator during the 0 to 24 hour time interval."); *see also id.*, Table 3. Aloxi explained that "a single dose of ALOXI Capsules 0.5 mg was numerically similar to a single dose of I.V. ALOXI 0.25 mg" even though "statistical non-inferiority was not demonstrated." *Id.*, 4. With regard to additional evaluated endpoints, Aloxi describes "the proportion of patients with complete response at 0-120 hours was 58.8% versus 59.3%, respectively" and the "proportions of patients

with no nausea at 0-24 and 24-120 hours were also numerically similar between oral and I.V. doses." *Id.*

107. Ample evidence shows Aloxi (and the disclosure therein) was publicly available prior to the critical date. For example, the U.S. Government website, DailyMed, posted the Aloxi label on October 30, 2008. Webpage printouts of the DailyMed website are provided in EX1053, which show the main page of the DailyMed website (EX1053, 1-3) and an announcement explaining date-specific searching of published drug labels (EX1053, 4). DailyMed explains users can retrieve "active labels published on" a given date on the website. EX1053, 4. A search using this function for palonosetron labels published by October 30, 2008, yields two results: the intravenous palonosetron hydrochloride (posted to DailyMed on October 19, 2007) and the orally administered palonosetron hydrochloride capsules disclosed by EX1015 (posted to DailyMed on October 30, 2008). EX1053, 5. Selecting the Aloxi (palonosetron hydrochloride) capsule label provides a web-formatted version of the revised 09/2008 drug label, providing substantively the same information as Aloxi with a minor correction. *Id.*, 6-16. Thus, DailyMed (EX1053) illustrates the public availability of Aloxi and the information contained therein.

108. An Internet Archive capture of DailyMed further confirms public availability prior to the critical date. Webpage printouts of the Internet Archive

capture of DailyMed are provided in EX1054, which show the main page of the DailyMed website as of November 12, 2008, including the ability to search by drug name or to browse drug labels alphabetically. EX1054, 1. Selecting the "P" category yields a website captured January 17, 2009, presenting drug package labels beginning with the letter "P." *Id.*, 2. Aloxi (palonosetron hydrochloride) capsule is present on this list. *Id.*, 3. Selecting the Aloxi (palonosetron hydrochloride) capsule label provides a web-formatted version of the drug label captured May 21, 2009, providing substantively the same information as Aloxi. *Id.*, 21-32. Thus, the Internet Archive capture of DailyMed (EX1054) illustrates the public availability of Aloxi and the information contained therein.

109. Additional websites affirmed the public availability of the Aloxi capsules label and the information therein prior to the critical date. For example, an Internet Archive capture of the website, "RxList", shows that as of September 24, 2008, the information from Aloxi was reproduced and publicly available. EX1052. An Internet Archive capture of the main page of the RxList website dated September 24, 2008, identifies the website as "The Internet Drug Index for prescription drugs and medications." EX1052, 1. The main page of the website identifies under "New Drugs at RxList" the Aloxi (palonosetron HCl) Capsules. *Id.* Selecting this link yields a website containing all information from the Aloxi drug label (EX1052, 11-26). Alternatively, the main page of RxList provides the ability

of a user to browse drugs by letter. EX1052, 1. Selecting the "P" category yields a list of drugs beginning with the letter P, including "Palonosetron HCl Capsules (Aloxi Capsules)." *Id.*, 3. Selecting this link also navigates to the website containing all information from the Aloxi drug label (EX1052, 11-26). EX1052 pages 11-26 is a print-out of the captured webpage for each of tabs 1-7, providing the details of Aloxi. The cumulative tabs of EX1052 provide substantively the same information as Aloxi. *Compare* EX1016 *with* EX1052 (RxList Tab 1 corresponds to Section 11 of the Aloxi Label; Tab 2 corresponds to Sections 1, 2, 16, and part of p. 6; Tab 3 corresponds to Sections 6-7; Tab 4 corresponds to Sections 5, 8, 13, and 17; Tab 5 corresponds to Section 10; Tab 6 corresponds to Sections 12 and 14; Tab 7 corresponds to Patient Information (pages 5-6)). Thus, the Internet Archive capture of RxList (EX1052) also illustrates the public availability of Aloxi and the information contained therein.[4]

110. Additionally, Patent Owner itself announced FDA approval of the palonosetron HCl capsules on August 23, 2008. EX1029 ("Eisai Corporation…and

[4] Throughout my Declaration, I refer to (and cite) exhibit EX1015 (the Aloxi label) first, but as described above, each of EX1054, EX1053, and EX1052 is substantively the same. These additional exhibits are submitted to corroborate public availability.

Helsinn Healthcare SA…announced on August 23rd (EST) that the U.S. Food and Drug Administration (FDA) has approved a new oral formulation of ALOXI® (palonosetron hydrochloride), a 5-hydroxytryptamine-3 (5-HT_3) receptor antagonist, for the prevention of chemotherapy-induced nausea and vomiting (CINV).”). Helsinn’s announcement explained that the “ALOXI Capsules 0.5 mg for oral administration is indicated for the prevention of acute nausea and vomiting following initial and repeated courses of moderately emetogenic chemotherapy” and confirms the capsules are “administered approximately one hour prior to the start of chemotherapy.” *Id.*

E. Herrstedt

111. Herrstedt (EX1010) is a scientific review article that published in the journal, BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY in 2007. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

112. Herrstedt provides a summary of treatments for chemotherapy-induced nausea and vomiting (CINV). EX1010 (Herrstedt), Abstract. It describes the development of antiemetic therapy including antagonists of the serotonin receptor 5-HT_3 (e.g., palonosetron, ondansetron) and of the NK_1 receptor antagonist (aprepitant). *Id.* Herrstedt explains the addition of the NK_1 receptor antagonist to standard chemotherapy antiemetic drug combination of 5-HT_3

receptor antagonist plus corticosteroid (e.g., dexamethasone) was beneficial. *Id.* ("Aprepitant increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or moderately emetogenic chemotherapy."). Herrstedt describes generally that antiemetic drugs should be administered in a combination therapy that includes a corticosteroid, a 5-HT$_3$ receptor antagonist, and an NK$_1$ receptor antagonist. *Id.*, 145.

113. Herrstedt also describes palonosetron as a new 5-HT$_3$ receptor antagonist. *Id.*, 145-146. Herrstedt states that palonosetron is "a very potent and specific binding at 5-HT3 receptors and a half-life around 40 hr as compared to less than 10 hr for the other agents (table 3)." *Id.*, 145; *see also* Table 3 (below).

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

Additionally, while other 5-HT$_3$ receptor antagonists showed "limited or no efficacy in delayed emesis" (i.e., emesis occurring in the 24-120 hour time window), Herrstedt explained that "Palonosetron might be an exception" because it had FDA approval "in the treatment of delayed emesis from MEC [moderately emetogenic chemotherapy]." *Id.*, 146.

114. Herrstedt provides a summary of multiple phase III clinical trials evaluating the efficacy of a drug dosing regimen including administration of a 5-HT_3 receptor antagonist (ondansetron), dexamethasone, and an NK_1 receptor antagonist (aprepitant). *Id.*, 146. It reports a statistical benefit was seen in these studies, evidencing the therapeutic application of the combined therapeutics as prophylaxis for nausea and vomiting associated with chemotherapy. *Id.*

115. Herrstedt also describes that the combination of the NK_1 receptor antagonist aprepitant "results in a two-time increase in the AUC [Area Under Curve] of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism." *Id.*, 147. In other words, the reference recognizes that when dexamethasone is administered with the NK_1 receptor antagonist (aprepitant), the concentration of dexamethasone doubles due to the prevention of dexamethasone metabolism. It would have been obvious for a POSA to decrease the dexamethasone dose accordingly to account for this interaction.

F. Hargreaves

116. Hargreaves (EX1012) is an article that published in the scientific journal, JOURNAL OF CLINICAL PSYCHIATRY in 2002. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

117. Hargreaves discloses the use of positron emission tomography (PET) to study the NK_1 receptor pathway and its association with Substance P, which is

implicated in pathophysiology of emesis and depression. EX1012 (Hargreaves), Abstract. Using the NK_1 receptor antagonist aprepitant, the study evaluated occupancy of NK_1 receptors within the brain and associated such occupancy with therapeutic effects. *Id.* Hargreaves describes that a 75% or greater NK_1 receptor occupancy was associated with blocked emesis. *Id.*, 23.

G. Herrington

118. Herrington (EX1016) is an article that published in the scientific journal, CANCER, on March 7, 2008. EX1016, 1 ("Published online 7 March 2008"). I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

119. Herrington discloses a clinical trial evaluating three different treatment arms for antiemetic therapeutic effect for patients receiving highly emetogenic chemotherapy. EX1016, Abstract. All treatment arms received a 0.25 mg dose of the 5-HT_3 receptor antagonist palonosetron intravenously on Day 1 (prior to chemotherapy), and all treatment arms also received dexamethasone administered on each of Days 1-4 (Arms A & B: 12 mg on Day 1, 8 mg on Days 2-4; Arm C: 18 mg on Day 1; 8 mg on Days 2-4). *Id.* Arm A also received 125 mg orally administered aprepitant on Day 1 plus 80 mg orally administered aprepitant on Days 2-3. Arm B likewise received the standard 125 mg orally administered

aprepitant on Day 1 (prior to chemotherapy) but received placebo on days 2-3 in place of aprepitant. Arm C received placebos on days 1-3. *Id.*

120. Herrington discloses that a single day oral administration of a therapeutically effective amount of NK_1 receptor antagonist is as effective as administering over the course of multiple days. Herrington terminated the evaluation of Arm C due to poor control of emesis. *Id.* Herrington only advanced the studies where patients were receiving the triple therapy of NK_1 and 5-HT_3 receptor antagonists plus dexamethasone. From evaluation of the results, Herrington concluded:

> From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, ***a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

Id. Herrington notes a benefit of such single dose administration is that it "would equate to lower drug cost with similar effectiveness." *Id.*, 2086. A skilled artisan would have also known that convenience and patient preference were benefits of single dose administration.

121. Herrington also discloses that there was no significant difference between participants receiving a single (Day 1, 125 mg) dose of the NK_1 receptor antagonist and those receiving the NK_1 receptor antagonist for multiple days for both the ***acute phase*** (i.e., 0-24 hours following chemotherapy) and the ***delayed***

phase (i.e., 24-120 hours following chemotherapy). *See, e.g.*, EX1016, Table 3 reproduced below.

TABLE 3
Proportion of Patients With No Emesis

	Percentage with no emesis				
	Arm A Palonosetron plus 3-day aprepitant, n = 28	Arm B Palonosetron plus 1-day aprepitant, n = 27	Asymptotic 95% CI*	P†	Arm C Palonosetron plus placebo, n = 16
Acute phase	96.4	100	(−10.5–3.3)	1.00	93.8
Delayed phase	92.9	92.6	(−13.5–14.0)	1.00	50.0
Both phases	92.9	92.6	(−13.5–14.0)	1.00	50.0

* Difference between 3-Day and 1-Day aprepitant.
† Fisher Exact test was used (3-Day vs 1-Day).

122. Herrington describes that there were likewise "no statistically significant differences" difference between the single day administration of aprepitant (Arm B) and the multiple day administration of aprepitant (Arm A) for prevention of significant nausea. *Id.*, 2084 & Fig. 2. Herrington's single administration of aprepitant (125 mg) differed from Grunberg's large dose of aprepitant (285 mg), as I described above. *See* Section IV; *see also* Section XXXI.A.2.

H. Bonadeo

123. International patent publication number WO 2008/049552 to Bonadeo et al. ("Bonadeo") (EX1017) published on May 2, 2008. I understand it is prior art that published before the earliest possible priority date of November 18, 2009.

124. Bonadeo describes soft capsule formulations of palonosetron hydrochloride for oral administration. EX1017 (Bonadeo), Title, Abstract. Bonadeo states its solid dosage form of palonosetron hydrochloride has improved stability and bioavailability, and "are preferably in the form of liquid filled capsules." EX1017 (Bonadeo), Abstract. Bonadeo identifies degradation products of palonosetron including "an oxygen mediated degradation product [that] is referred to herein as 'Cpd1.'" *Id.*, 3. Bonadeo's Cpd1 is (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate, as detailed by Bonadeo. *Id.*, 11. Teaching its "dosage forms have excellent stability over prolonged periods of time, excellent resistance to oxidative degradation, and excellent bioavailability when orally ingested" and that the capsules "are preferably used for the treatment of emesis," describing embodiments "wherein said palonosetron comprises Cpd1 in an amount of less than 1.0 wt%." *Id.*, 3.

X. CLAIM CONSTRUCTION

125. I have been advised that the claims should be understood according to their ordinary and customary meaning as understood by a person having ordinary skill in the art at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have applied the plain and ordinary meaning of the claims in my analysis below. Additionally, the

specification and prosecution history discuss the meaning ascribed to some claim terms, and I address these terms when discussing the corresponding claims.

126. I understand that the term "comprising" in a claim indicates that the claim includes at least the listed elements, but that the claim can also encompass additional, unstated elements.

XI. ['826 PATENT GROUND 1] '826 PATENT CLAIMS 19, 22-23 & 25 WERE OBVIOUS OVER MASCC AND HOFFMANN.

127. For the reasons discussed in detail below, it is my opinion that each of claims 19, 22-23 and 25 of the '826 patent was obvious as a whole. The obviousness of claims 19, 22-23 and 25 is exemplified by disclosures in the MASCC and Hoffmann references.

128. I have evaluated below whether the combination of MASCC and Hoffmann discloses each and every element of each of claims 19, 22-23 and 25 of the '826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

129. As a high-level summary, MASCC discloses methods of treating both nausea and vomiting in human subjects in need of such antiemetic treatment during both the acute and the delayed phases of chemotherapy induced nausea and

vomiting in response to emetogenic chemotherapy. EX1013 (MASCC), 22. MASCC describes a combination antiemetic therapy administered in response to highly or moderately emetogenic chemotherapy, the prophylactic therapy comprising pre-administration of an NK_1 receptor antagonist in combination with dexamethasone and a 5-HT_3 receptor antagonist. *Id.*, 23. MASCC explains that the addition of an NK_1 receptor antagonist enhanced efficacy as compared to the latter two components alone. *Id.* MASCC specifically describes administering to the subject, prior to chemotherapy, an effective amount of the NK_1 receptor antagonist aprepitant. *Id.* MASCC explains that aprepitant is merely the first of this new class of selective NK_1 receptor antagonists to be employed in this combination. *Id.*, 22. MASCC also advocated for use of palonosetron as the 5-HT_3 receptor antagonist in the combination. EX1013 (MASCC), 24. Hoffmann describes netupitant as a new NK_1 receptor antagonist. EX1011 (Hoffmann), Abstract, 1364. It is my opinion that it would have been obvious to a POSA to employ the second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in MASCC.

130. The sections below explain in more detail how MASCC and Hoffmann disclose each and every element of claims 19, 22-23 and 25. I first analyze independent claim 19 of the challenged ’826 patent. Thereafter, I analyze dependent claims 22-23 and 25.

A. Claim 19

> **19[pre].** A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising

131. I have reproduced above the preamble of claim 19 of the ’826 patent. MASCC teaches a “method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy,” as recited in the preamble of claim 19. E.g., EX1013 (MASCC), 22 (“Therefore, to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given prior to chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).”). Accordingly, MASCC discloses the subject matter recited in the preamble of claim 19.

> **19[a].** administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and

132. I have reproduced above the administering step [a] element of claim 19. It is my opinion that MASCC in combination with Hoffmann teaches or suggests the administering step [a] of claim 19.

133. As I have discussed above, MASCC discloses administering therapeutically effective amounts of a combination of three antiemetic drugs to a human subject in need of treating for both nausea and vomiting during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy. EX1013 (MASCC), 22-24. For example, MASCC explicitly recommends administering therapeutically effective amounts of three drugs in combination for treating acute-phase nausea and vomiting that occurs after highly emetogenic chemotherapy. This three-drug combination includes therapeutically effective amounts of: (1) a 5-HT_3 receptor antagonist (e.g., ondansetron or palonosetron); (2) an NK_1 receptor antagonist (aprepitant); and (3) dexamethasone. EX1013 (MASCC), 22; *see also id.* 23 ("patients receiving cisplatin treated with a combination of aprepitant, a 5-HT3-receptor antagonist and dexamethasone to prevent acute vomiting and nausea"). The recommendation explicitly describes that this therapy is to be administered prior to chemotherapy, thereby treating acute-phase nausea and vomiting. *Id.* 22. In MASCC, the therapeutically effective amount of NK_1 receptor antagonist administered on day 1 is 125 mg of aprepitant, delivered orally. *Id.*

134. Though the specific NK_1 receptor antagonist administered in MASCC was aprepitant, not netupitant, MASCC also teaches that aprepitant was merely the first in this new class of selective NK_1 receptor antagonists. EX1013 (MASCC), 22

("Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK_1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P.").

135. Hoffmann not only discloses netupitant as a selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant as an "excellent" alternative to aprepitant for NK_1 receptor antagonism. For example, in Hoffmann:

> The evaluation of this [NK_1 receptor antagonist] class is briefly outlined, leading to the identification of netupitant 21[, one of] two new proprietary chemical entities with high affinity and excellent CNS penetration.

EX1011 (Hoffmann), Abstract.

136. It is my opinion that a POSA would have understood Hoffmann as providing good reason to replace the therapeutically effective amount of NK_1 receptor antagonist (aprepitant) in MASCC with a therapeutically effective amount of the second generation NK_1 receptor antagonist from Hoffmann (netupitant) to achieve similar or better efficacy in CINV. Indeed, MASCC identified the class of NK_1 receptor antagonists as useful for this purpose and identified aprepitant as just the first species of this new class, while Hoffmann identified netupitant as an attractive NK_1 receptor antagonist for replacing aprepitant. Moreover, a POSA would have understood that netupitant's excellent CNS penetration described by

Hoffmann was highly desirable in NK_1 receptor antagonists for anti-emetogenic therapy, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. Indeed, the prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant) described in Hoffmann, for

the first generation NK_1 receptor antagonist (aprepitant) in MASCC's antiemetic therapy with a reasonable expectation of success. It is my opinion that a POSA would have had an extremely high likelihood of succeeding in substituting netupitant for aprepitant for antiemetic combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism) when administered prior to chemotherapy.

137. Hoffmann also disclosed that an additional benefit of using netupitant as the NK_1 receptor antagonist is that it worked excellently when a therapeutically effective amount was administered orally:

> Preferred compounds were tested for their potential to pharmacologically block central NK_1 receptors in gerbils. Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK_1-selective receptor agonist GR73632. Excellent oral antagonist activity was observed for the pyridine derivatives from class E as exemplified for netupitant (**21**)….

EX1011 (Hoffmann), 1364.

138. A POSA would have recognized that the ability to administer the NK_1 receptor antagonist orally was advantageous because:

> At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are ***less costly and more convenient***; for those reasons, they are

recommended over intravenous therapy.

EX1018 (Gralla), 2976. The POSA would have understood that oral administration is simpler, less costly, more convenient, and more preferred than intravenous administration.

139. It would have been routine for a POSA in view of the disclosures of MASCC and Hoffmann to perform a dose-ranging study, substituting netupitant for aprepitant as the NK_1 receptor antagonist in the three-drug combination. For example, MASCC teaches that when determining a therapeutically effective amount of NK_1 receptor antagonist, a randomized study may be used with doses ranging over approximately an order of magnitude to determine what dose "had 'the most favorable benefit:risk profile.'" EX1013 (MASCC), 22. Hoffmann described netupitant's efficacy using in vivo studies, which a POSA would have understood as a starting point for developing a dose range that would scale upwards to likewise determine a favorable benefit:risk profile for the therapeutically effective dose for treating emesis. A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating CINV.

140. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '826 patent. The '826 patent specification, for example, explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1001 ('826 patent), 7:55-61. Therefore, the '826 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. Just as admitted in the specification of the challenged patent, a skilled artisan would have found it routine to arrive at a therapeutic dose of netupitant, and in view of MASCC (using therapeutic amounts of each antiemetic drug), the POSA would have had good reason (without the benefit of the challenged patent) to administer the therapeutically effective amount with a reasonable expectation that it would treat CINV.

141. Accordingly, MASCC discloses administering to said subject before said chemotherapy a therapeutically effective amount of an NK_1 receptor antagonist (aprepitant), Hoffmann discloses administering an effective amount of netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of netupitant for treatment of CINV, such as in the method disclosed in MASCC.

> **19[b].** a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.

142. I have reproduced above the administering step [b] element of claim 19 of the challenged ’826 patent. This element recites the use of a known pharmaceutical agent for its known purpose, and MASCC discloses this element.

143. For example, MASCC’s three-drug combination for treating acute-phase nausea and vomiting that occurs after highly emetogenic chemotherapy includes administering a 5-HT_3 receptor antagonist. EX1013 (MASCC), 22-23. Indeed, MASCC specifically discloses administering a therapeutically effective amount of palonosetron as the 5-HT_3 receptor antagonist. For example, MASCC states:

> Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists. Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases[.]

EX1013 (MASCC), 24. MASCC thus clearly and explicitly discloses using a therapeutically effective amount of palonosetron as the 5-HT_3 receptor antagonist for treating CINV.

144. The combination of MASCC and Hoffmann thus teaches all of the elements of claim 19 and rendered the claim obvious as a whole.

B. Claim 22

> **22.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

145. Claim 22 additionally recites dexamethasone is administered in a subtherapeutic dosage amount. As I have previously addressed above, claim 19 was obvious over MASCC and Hoffmann.

146. MASCC describes, if the patient is undergoing highly emetogenic chemotherapy, administering dexamethasone on days one, two, three and four, wherein day one is the day on which the NK_1 and 5-HT_3 receptor antagonists are administered:

> Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2-4 with ***a three-drug regimen*** of ondansetron 32 mg, ***dexamethasone 12 mg*** and aprepitant 125 mg ***on day 1***, followed by ***dexamethasone 8 mg daily on days 2-4*** and aprepitant 80 mg days 2 and 3. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased dexamethasone levels approximately two-fold.

EX1013 (MASCC), 22. Said studies were conducted in patients undergoing highly emetogenic chemotherapy (i.e., cisplatin). EX1013 (MASCC), 22.

147. MASCC teaches 20 mg of dexamethasone was considered the standard therapeutically effective dose for highly emetogenic chemotherapy. EX1013 (MASCC), 22. MASCC Table 3 explicitly teaches dexamethasone is orally administered in a 20 mg dose for patients not receiving aprepitant. *Id.*, Table 3. I understand the '826 patent admits this minimum was already known in the field:

> The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1001 ('826 patent), 7:62-8:4 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). The 12 mg and 8 mg dexamethasone doses on days 1-4 thus satisfy the sub-therapeutic limitation of claim 22. MASCC explains that NK_1 antagonists such as aprepitant make dexamethasone twice as effective, thus its dose is reduced accordingly. *Id.*

148. I explained above why a POSA would have been motivated to administer Hoffmann's netupitant as the NK_1 antagonist and MASCC's

palonosetron as the 5-HT_3 antagonist. *See* Section XI.A, above. The POSA would have had good reason to prophylactically administer therapeutically effective amounts of the NK_1 and 5-HT_3 receptor antagonists on day 1 (prior to chemotherapy) as disclosed in MASCC because MASCC recommends the therapeutics should be "given before chemotherapy." EX1013 (MASCC), 22; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 receptor antagonist and NK_1 receptor antagonist administered on Day 1 provided antiemetic effect). The POSA would have had a reasonable expectation of success in substituting netupitant as the NK_1 antagonist and palonosetron as the 5-HT_3 antagonist, as I explained above. *See* Section XI.A.

149. Accordingly, it is my opinion that claim 22 as a whole was also obvious over MASCC and Hoffmann.

C. Claim 23

> **23.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

150. Claim 23 additionally recites dexamethasone is administered 12 mg on day one and 8 mg on days 2-4. As I have previously addressed above, claim 19 was obvious over MASCC and Hoffmann.

151. MASCC describes, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which the NK_1 and 5-HT_3 receptor antagonists are administered. For example, MASCC teaches for patients undergoing highly emetogenic chemotherapy:

> Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2–4 with a three-drug regimen of ondansetron 32 mg, ***dexamethasone 12 mg*** and aprepitant 125 mg ***on day 1, followed by dexamethasone 8 mg daily on days 2–4*** and aprepitant 80 mg days 2 and 3. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased dexamethasone levels approximately two-fold.

EX1013 (MASCC), 22. Said studies were conducted in patients undergoing highly emetogenic chemotherapy (i.e., cisplatin). EX1013 (MASCC), 22. MASCC also explains dexamethasone is orally administered. *Id.*, Table 3. As I explained above, MASCC describes day one is the day on which NK_1 and 5-HT_3 receptor antagonists are administered, and a POSA would have had good reason—and a reasonable expectation of success—in administering Hoffmann's netupitant for the NK_1 receptor antagonist, and

MASCC's palonosetron as the 5-HT_3 receptor antagonist. Section XI.A, above.

152. Accordingly, it is my opinion that claim 23 was obvious as a whole over MASCC and Hoffmann.

D. Claim 25

> **25.** The method of claim 19, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK_1 activity.

153. Claim 25 depends from claim 19 and further requires that palonosetron and netupitant are "synergistically effective to antagonize NK_1 activity." I see no definition of "synergistically effective to antagonize NK_1 activity" in the '826 patent. Nor do I see disclosure of synergy in the specification. But any alleged synergistic effect is an inherent quality of palonosetron and netupitant being co-administered in therapeutic amounts. Patent applicant asserted as much during prosecution of the '050 application. EX1008 (file history of '050 application), 186 ("At ***all*** concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined."). As I described above, the combination of MASCC and Hoffmann rendered obvious co-administering netupitant and palonosetron. *See* Section XI.A, above.

154. In addition to the inherency admission by the patentee before the Patent Office, recent studies also confirm any synergy is inherent to the co-administration that I've explained above was obvious. The literature reasons that "both netupitant and palonosetron can trigger NK_1 receptor internalization." EX1045 (Thomas), 2643; *see also id.*, 2642. Palonosetron—a 5-HT_3 receptor antagonist—affects NK_1 receptors "through a 5-HT_3 receptor-mediated effect" between the 5-HT_3 and NK_1 receptors. *Id.* The literature identifies this internalization as "***a mechanistic explanation of*** the additive and ***synergistic effects*** on the NK_1 receptor antagonism when a combination of netupitant and palonosetron is used in these cells." *Id*. (emphasis added); *see also* EX1041 (Rojas), 365, 368 (unlike other 5-HT_3 receptor antagonists, palonosetron triggered internalization of 5-HT_3 receptors, affecting the "5-HT3 and NK-1 receptor pathways in a dose- and time-dependent fashion"). These post-critical date publications identify the NK_1-receptor-internalization-property of palonosetron as a property intrinsic to that prior art 5-HT_3 receptor antagonist. Any alleged additive or synergistic effect on NK_1 receptor antagonism is thus inherent to the obvious combination of therapeutically-effective amounts of palonosetron and an NK_1 receptor antagonist.

155. Because the additive/synergistic effect is an inherent property that naturally results from administering therapeutically effective amounts of

palonosetron and an NK_1 receptor antagonist—a combination that MASCC teaches is favorable particularly for palonosetron's additional efficacy for treating delayed emesis—this allegedly unexpected result is merely an inherent property of a prior art or at least an obvious combination.

156. Accordingly, it is my opinion that claim 25 was obvious as a whole over MASCC and Hoffmann.

E. Motivation to Combine

157. By November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the triple antiemetic combination therapy provided in MASCC, using therapeutically effective amounts of the new NK_1 and 5-HT_3 receptor antagonists as claimed.

158. As an initial matter, persons having ordinary skill in the art would have had good reason to prophylactically (i.e., before the administration of chemotherapy) treat patients receiving highly and moderately emetogenic chemotherapy with therapeutically effective amounts of the MASCC triple therapy to provide antiemetic effect. MASCC describes the three-drug antiemetic combination of 5-HT_3 receptor antagonist (ondansetron), NK_1 receptor antagonist (aprepitant), and dexamethasone yielded superior response rates (no emesis, no use

of rescue antiemetics) compared to the two-drug combination lacking an NK_1 receptor antagonist. EX1013 (MASCC), 22. "Additional analysis confirmed that the aprepitant combination was significantly superior during six cycles of chemotherapy." *Id.* MASCC describes the three-drug antiemetic combination as administered on Day 1. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (known to administer a therapeutically effective amount of therapeutics including NK_1 receptor antagonist on Day 1 prior to chemotherapy (see, e.g., EX1013 (MASCC) Table 3)).

159. A person having ordinary skill in the art would have employed the new 5-HT_3 receptor antagonist, palonosetron, in the three-drug combination therapy, for its enhanced efficacy targeting the same mechanistic pathway, as disclosed in MASCC. For example, palonosetron was known to have "a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists." EX1013 (MASCC), 24. Specifically, palonosetron was equal to or better than the 5-HT_3 receptor antagonists dolasetron or ondansetron "in both the acute and delayed phases." *Id.* Thus, there was good reason to employ palonosetron as the 5-HT_3 receptor antagonist, instead of ondansetron, because it would have a longer half-life and improved binding. Additionally, palonosetron was known to be available in an oral formulation (0.56 mg palonosetron HCl). EX1015 (Aloxi); EX1052 (RxList); EX1053 (DailyMed); EX1054 (DailyMed

Archived). A POSA would have been motivated to administer to the patient the oral form of palonosetron HCl as the 5-HT_3 receptor antagonist for ease to both patient and practitioner, as well as for improved patient perception and comfort, as described above.

160. A person having ordinary skill in the art also would have employed the second generation NK_1 receptor antagonist, netupitant, in the MASCC triple therapy. A POSA would have sought to modify the therapeutic antiemetic drug combination of MASCC with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. A POSA thus would have had good reason to modify the MASCC antiemetic drug combination to replace the NK_1 receptor antagonist aprepitant with Hoffmann's NK_1 receptor antagonist netupitant because, as Hoffmann explains, netupitant was shown "to potently inhibit NK_1 agonist-induced foot tapping…after oral administration" which was indicative of successful NK_1 receptor antagonism, and also identified netupitant as having "[e]xcellent oral antagonist activity." EX1011 (Hoffmann), 1364-1365; *see also* EX1014 (Bös), 1:15-2:65, 14:9-38, 18:42-19:25 (disclosing netupitant as next-generation, NK_1 receptor antagonist having high receptor affinity associated with increased (24-30-hour) half-life, useful for anti-emesis combination treatment). Thus, netupitant was known to be a second-generation NK_1 receptor antagonist, and the POSA would have sought to replace aprepitant with a therapeutically-

effective amount of netupitant and would have had a reasonable expectation of success in doing so.

161. Accordingly, persons having ordinary skill in the art would have had good reason to modify the MASCC triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Hoffmann's second-generation NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

F. Reasonable Expectation of Success

162. Persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success employing the MASCC triple active combination therapy with the claimed netupitant and palonosetron therapeutics. MASCC teaches that persons having ordinary skill in the art had used alternative 5-HT_3 receptor antagonists to treat CINV. EX1013 (MASCC), 22. MASCC describes its treatment administers the therapeutics on Day 1 prior to chemotherapy. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (therapeutically effective amount of therapeutics including NK_1 receptor administered on Day 1 afforded antiemetic effect). MASCC explicitly envisions the substitution of palonosetron, the "new 5-HT3-receptor agent" and other therapeutic agents into the MASCC antiemetic drug combination. *Id.*, 25. Furthermore, the person having

ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome. Because both palonosetron and ondansetron were known to achieve the desired therapeutic effect via the same mechanism—by antagonizing the 5-HT_3 receptor—the POSA would have expected therapeutically effective amounts of palonosetron and ondansetron to achieve at least a comparable effect of anti-emesis. EX1013 (MASCC), 23-24. That palonosetron was known to have favorable qualities as compared to ondansetron (as I describe above) means the POSA would have reasonably expected that palonosetron would improve or be similar to the MASCC antiemetic drug combination as compared to the standard therapy (using ondansetron, without NK_1 receptor antagonist).

163. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. MASCC recognized that "Aprepitant is the first of a new class of drugs" and thus envisioned additional members of that class likely would follow, which would likewise be included in the MASCC antiemetic drug combination. *Id.*, 22. Both

netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1011 (Hoffmann), 1362; *see also* EX1014 (Bös), 1:15-2:65, 14:9-38, 18:42-19:25. Thus, a POSA would have reasonably expected therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would improve or be similar to the MASCC antiemetic drug combination as compared to the standard therapy (using ondansetron, without NK_1 receptor antagonist).

164. Accordingly, the POSA had good reason to combine MASCC and Hoffmann to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XII. ['826 PATENT GROUND 2] '826 PATENT CLAIMS 19-20, 22-23 & 25 WERE OBVIOUS OVER MASCC AND BÖS.

165. For the reasons discussed in detail below, it is my opinion that each of claims 19-20, 22-23 and 25 of the '826 patent was obvious as a whole. The obviousness of claims 19-20, 22-23 and 25 is exemplified by disclosures in the MASCC and Bös references.

166. I have evaluated below whether the combination of MASCC and Bös discloses each and every element of each of claims 19-20, 22-23 and 25 of the '826

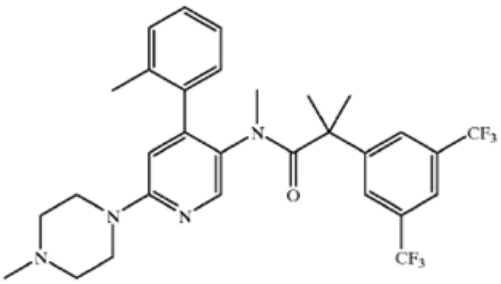
patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

167. As I described above (Section XI), MASCC discloses methods of treating both nausea and vomiting in human subjects in need of such antiemetic treatment during both the acute and the delayed phases of chemotherapy induced nausea and vomiting in response to emetogenic chemotherapy. *See also* EX1013 (MASCC), 22. MASCC describes a combination antiemetic therapy administered in response to highly or moderately emetogenic chemotherapy, the prophylactic therapy comprising pre-administration of an NK_1 receptor antagonist in combination with dexamethasone and a 5-HT_3 receptor antagonist. *Id.*, 23. MASCC explains that the addition of an NK_1 receptor antagonist enhanced efficacy as compared to the latter two components alone. *Id.* MASCC specifically describes administering to the subject, prior to chemotherapy, an effective amount of the NK_1 receptor antagonist aprepitant. *Id.* MASCC explains that aprepitant is merely the first of this new class of selective NK_1 receptor antagonists to be employed in this combination. *Id.*, 22. MASCC also advocated for use of palonosetron as the 5-HT_3 receptor antagonist in the combination. EX1013

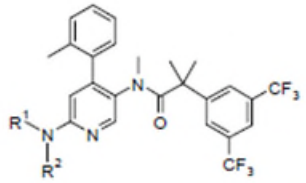
(MASCC), 24. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

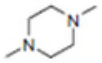
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*, 17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in Gerbil and blocks emesis in Ferrets and sancus murinus with similar potency."). As a POSA would have recognized, Bös formula Ib is netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1

receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in MASCC.

168. The sections below explain in more detail how MASCC and Bös disclose each and every element of claims 19-20, 22-23 and 25. I first analyze independent claim 19 of the challenged ’826 patent. Thereafter, I analyze dependent claims 20, 22-23 and 25.

A. Claim 19

> **19[pre].** A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising

169. I have reproduced above the preamble of claim 19 of the ’826 patent. MASCC teaches a “method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy,” as recited in the preamble of claim 19. E.g., EX1013 (MASCC), 22 (“Therefore, to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT3-receptor antagonist, dexamethasone and aprepitant given prior to chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high).”). Accordingly, MASCC discloses the subject matter recited in the preamble of claim 19.

19[a]. administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and

170. I have reproduced above the administering step [a] element of claim 19. It is my opinion that MASCC in combination with Bös teaches or suggests the administering step [a] of claim 19.

171. As I have discussed above, MASCC discloses administering therapeutically effective amounts of a combination of three antiemetic drugs to a human subject in need of treating for both nausea and vomiting during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy. EX1013 (MASCC), 22-24. For example, MASCC explicitly recommends administering therapeutically effective amounts of three drugs in combination for treating acute-phase nausea and vomiting that occurs after highly emetogenic chemotherapy. This three-drug combination includes therapeutically effective amounts of: (1) a 5-HT_3 receptor antagonist (e.g., ondansetron or palonosetron); (2) an NK_1 receptor antagonist (aprepitant); and (3) dexamethasone. EX1013 (MASCC), 22; *see also id.*, 23 ("patients receiving cisplatin treated with a combination of aprepitant, a 5-HT3-receptor antagonist and dexamethasone to prevent acute vomiting and nausea"). The recommendation explicitly describes that this therapy is to be administered prior to chemotherapy, thereby treating acute-phase nausea and vomiting. *Id.* 22. In

MASCC, the therapeutically effective amount of NK_1 receptor antagonist administered on day 1 (prior to chemotherapy) is 125 mg of aprepitant, delivered orally. *Id.*

172. Though the specific NK_1 receptor antagonist administered in MASCC was aprepitant, not netupitant, MASCC also teaches that aprepitant was merely the first in this new class of selective NK_1 receptor antagonists. EX1013 (MASCC), 22 ("Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK_1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P.").

173. Bös discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist useful for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> the most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous***

> ***system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

174. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective oral dose.

175. It is my opinion that a POSA would have understood Bös as providing good reason to replace the therapeutically effective amount of NK_1 receptor antagonist (aprepitant) in MASCC with a therapeutically effective amount of the second generation NK_1 receptor antagonist from Bös (netupitant) to achieve similar or better efficacy in CINV. Indeed, MASCC identified the class of NK_1 receptor antagonists as useful for this purpose and identified aprepitant as just the first species of this new class, while Bös identified netupitant as an attractive oral replacement for aprepitant. Moreover, a POSA would have understood that CNS penetration described by Bös was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. Indeed, the prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus

> tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant) described in Bös, for the first generation NK_1 receptor antagonist (aprepitant) in MASCC's antiemetic therapy combination with a reasonable expectation of success. Further, it is my opinion that a POSA would have had an extremely high likelihood of succeeding in substituting netupitant for aprepitant for antiemetic combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism) when administered prior to chemotherapy.

176. Bös also disclosed that an additional benefit of using netupitant as the NK_1 receptor antagonist is that it worked excellently when a therapeutically effective amount was administered orally before administration of highly emetogenic chemotherapy (e.g., cisplatin):

> ***Emesis was induced*** in ferrets by various emetogens (apomorphine,

> morphine, ipecauanha, ***cisplatin*** and $CuSO_4$. Pretreatment of this compound [netupitant] (0.3 mg/kg, p.o.) 2 hours before the emet[o]gen, ***completely blocked the emesis*** induced by all emetogens.

Id., 19:11-20 (emphasis added).

177. A POSA would have recognized that the ability to administer the NK_1 receptor antagonist orally was advantageous because:

> At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are ***less costly and more convenient***; for those reasons, they are recommended over intravenous therapy.

EX1018 (Gralla), 2976. The POSA would have understood that oral administration is simpler, less costly, more convenient, and more preferred than intravenous administration.

178. It would have been routine for a POSA in view of the disclosures of MASCC and Bös to perform a dose-ranging study, substituting netupitant for aprepitant as the NK_1 receptor antagonist in the three-drug combination. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). Further, MASCC teaches that when determining a therapeutically effective amount of NK_1 receptor antagonist, a randomized study may be used with doses ranging over approximately an order of magnitude to determine what dose "had 'the most favorable benefit:risk profile.'" EX1013

(MASCC), 22. A POSA would have had good reason to implement such a randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile. A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating CINV.

179. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the ’826 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the ’826 patent specification, which explains:

> As used herein, “therapeutically effective amount” refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1001 (’826 patent), 7:55-61. Therefore, the ’826 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the therapeutic dose of netupitant, and in view of MASCC (using therapeutic amounts of each antiemetic drug), the POSA would have had good reason to

prophylactically administer the therapeutically effective amount with a reasonable expectation that it would treat CINV.

180. Accordingly, MASCC discloses administering to said subject before said chemotherapy a therapeutically effective amount of an NK_1 receptor antagonist (aprepitant), Bös discloses administering an effective amount of netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of netupitant for treatment of CINV, such as in the method disclosed in MASCC.

19[b]. a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.

181. I have reproduced above the administering step [b] element of claim 19 of the challenged ’826 patent. This element recites the use of a known pharmaceutical agent for its known purpose, and MASCC discloses this element.

182. For example, MASCC’s three-drug combination for treating acute-phase nausea and vomiting that occurs after highly emetogenic chemotherapy includes administering a 5-HT_3 receptor antagonist. EX1013 (MASCC), 22-23. Indeed, MASCC specifically discloses administering a therapeutically effective amount of palonosetron as the 5-HT_3 receptor antagonist. For example, MASCC states:

> Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor

> antagonists. Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases[.]

EX1013 (MASCC), 24. It is my opinion that MASCC clearly and explicitly discloses using a therapeutically effective amount of palonosetron as the 5-HT3 receptor antagonist for treating CINV.

183. The combination of MASCC and Bös thus teaches all of the elements of claim 19 and rendered the claim obvious as a whole.

B. Claim 20

> **20.** The method of claim 19, comprising orally administering from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically acceptable salt thereof.

184. Claim 20 additionally recites that the netupitant is orally administered in an amount of about 200 to about 400 mg, and that the palonosetron is orally administered in an amount of about 0.25 to about 0.75 mg. As I have previously addressed above, claim 19 was obvious over MASCC and Bös.

185. MASCC teaches administering palonosetron in an amount within the range of from about 0.25 to about 0.75 mg. MASCC explains:

> Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy with a single intravenous dose of

> ***palonosetron 0.25 mg*** that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases[.]

EX1013 (MASCC), 24; *see also id.*, Table 4. MASCC also teaches that oral administration of 5-HT_3 antagonists (e.g., ondansetron, palonosetron) was just as efficacious as intravenous dosing. EX1013 (MASCC), 24 ("Furthermore, there is no difference in the efficacy of oral or iv administration of a 5-HT3-receptor antagonist (palonosetron is only [commercially] available as an iv formulation and is further discussed below)."). As I explained above, the POSA would have understood that oral administration is simpler, less costly, more convenient, and more preferred than intravenous administration. Thus, in my opinion, a POSA would have had good reason to orally administer palonosetron or a pharmaceutically acceptable salt as the 5-HT_3 antagonist based on the disclosure of MASCC.

186. Bös teaches orally administering the family of NK_1 receptor antagonists—including netupitant—in amounts ranging from about 200 to about 400 mg of netupitant:

> In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Additionally, as I described above, Bös provides good reason to employ netupitant as MASCC's NK_1 receptor antagonist. Section XII.A, above. The POSA also would have had good reason to orally administer netupitant because Bös describes in vivo testing with oral administration of netupitant provided good antagonist activity. EX1014 (Bös), 18:64-19:10 (gerbils), 19:11-20 (ferrets), 19:21-24 (Suncus murinus). It is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., about 10 to 1,000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts. It is my opinion that the POSA would have had good reason to optimize Bös' range (including from about 200 to about 400 mg) when determining the therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

187. A POSA would have thus had good reason to administer each of the therapeutic agents in an oral form. As I explained above, oral administration (e.g., with a pill) is both simpler, less costly, and more convenient and more preferred than intravenous administration. MASCC describes dexamethasone is orally

administered (EX1013 (MASCC), Tables 3-4), and Bös teaches oral administration of NK_1 receptor antagonists including netupitant (EX1014 (Bös) 42:5-11), which in my opinion provides additional reason to administer palonosetron in an oral form, to keep all three administered therapeutics in the combination in the same form and enhancing ease of use by administrator and patient. It is my opinion that a POSA thus had good reason to administer the claimed drugs orally and in appropriate therapeutic doses and would have done so with a reasonable expectation of success.

188. Accordingly, it is my opinion that claim 20 as a whole was also obvious over MASCC and Bös.

C. Claim 22

> **22.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

189. Claim 22 additionally recites dexamethasone is administered in a subtherapeutic dosage amount. As I have previously addressed above, claim 19 was obvious over MASCC and Bös.

190. MASCC describes, if the patient is undergoing highly emetogenic chemotherapy, administering dexamethasone on days one, two, three and four,

wherein day one is the day on which the NK_1 and 5-HT_3 receptor antagonists are administered:

> Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2-4 with ***a three-drug regimen*** of ondansetron 32 mg, ***dexamethasone 12 mg*** and aprepitant 125 mg ***on day 1***, followed by ***dexamethasone 8 mg daily on days 2-4*** and aprepitant 80 mg days 2 and 3. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased dexamethasone levels approximately two-fold.

EX1013 (MASCC), 22. Said studies were conducted in patients undergoing highly emetogenic chemotherapy (i.e., cisplatin). *Id.*, 22.

191. MASCC teaches 20 mg of dexamethasone was considered the standard therapeutically effective dose for highly emetogenic chemotherapy. EX1013 (MASCC), 22. MASCC Table 3 explicitly teaches dexamethasone is orally administered in a 20 mg dose for patients not receiving aprepitant. *Id.*, Table 3. I understand the ’826 patent admits this minimum was already known in the field:

> The minimum effective dose of dexamethasone, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be 20 mg. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two,

> three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the minimum effective dose of dexamethasone is 20 mg. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1001 ('826 patent), 7:62-8:4 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). The 12 mg and 8 mg dexamethasone doses on days 1-4 thus satisfy the sub-therapeutic limitation of claim 22. MASCC explains that NK_1 antagonists such as aprepitant make dexamethasone twice as effective, thus its dose is reduced accordingly. *Id.*

192. I explained above why a POSA would have been motivated to administer Bös' netupitant as the NK_1 antagonist and palonosetron as the 5-HT_3 antagonist. *See* Section XII.A, above. The POSA would have administered the NK_1 and 5-HT_3 receptor antagonists on day 1 as disclosed in MASCC because MASCC recommends the therapeutics should be "given before chemotherapy." EX1013 (MASCC), 22; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 receptor antagonist and NK_1 receptor antagonist administered on Day 1 prior to chemotherapy provided antiemetic effect). The POSA would have had a reasonable expectation of success in substituting netupitant as the NK_1 antagonist and palonosetron as the 5-HT_3 antagonist, as I explained above. *See* Section XII.A.

193. Accordingly, it is my opinion that claim 22 as a whole was also obvious over MASCC and Bös.

D. Claim 23

> **23.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

194. Claim 23 additionally recites dexamethasone is administered 12 mg on day one and 8 mg on days 2-4. As I have previously addressed above, claim 19 was obvious over MASCC and Bös.

195. MASCC describes, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which the NK_1 and 5-HT_3 receptor antagonists are administered. For example, MASCC teaches for patients undergoing highly emetogenic chemotherapy:

> Two phase III trials with identical design compared a standard two-drug regimen with ondansetron 32 mg plus dexamethasone 20 mg on day 1, followed by dexamethasone 8 mg twice a day on days 2–4 with a three-drug regimen of ondansetron 32 mg, ***dexamethasone 12 mg*** and aprepitant 125 mg ***on day 1, followed by dexamethasone 8 mg daily on days 2–4*** and aprepitant 80 mg days 2 and 3. A reduced dose of dexamethasone was given in combination with aprepitant because a prior pharmacokinetic study found that aprepitant increased

dexamethasone levels approximately two-fold.

EX1013 (MASCC), 22. Said studies were conducted in patients undergoing highly emetogenic chemotherapy (i.e., cisplatin). *Id*. MASCC also explains dexamethasone is orally administered. *Id.*, Table 3. As I explained above, MASCC describes day one is the day on which NK_1 and 5-HT_3 receptor antagonists are administered, and a POSA would have had good reason—and a reasonable expectation of success—in administering netupitant for the NK_1 receptor antagonist, and palonosetron as the 5-HT_3 receptor antagonist. *See* Section XII.A, above.

196. Accordingly, it is my opinion that claim 23 was obvious as a whole over MASCC and Bös.

E. Claim 25

> **25.** The method of claim 19, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK_1 activity.

197. Claim 25 depends from claim 19 and further requires that palonosetron and netupitant are "synergistically effective to antagonize NK_1 activity." As I explained above, I see no definition of "synergistically effective to antagonize NK_1 activity" in the '826 patent, nor do I see disclosure of synergy in the specification. Section XI.D, above. Any alleged synergistic effect is an inherent quality of palonosetron and netupitant being co-administered in therapeutic

amounts. Patent applicant asserted as much during prosecution of the ’050 application. EX1008 (file history of ’050 application), 186 (“At ***all*** concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined.”). As I described above, the combination of MASCC and Bös rendered obvious co-administering netupitant and palonosetron. *See* Section XII.A, above.

198. In addition to the inherency admission by the patentee before the Patent Office, recent studies also confirm any synergy is inherent to the co-administration that I’ve explained above was obvious. The literature reasons that “both netupitant and palonosetron can trigger NK_1 receptor internalization.” EX1045 (Thomas), 2643; *see also id.*, 2642. Palonosetron—a 5-HT_3 receptor antagonist—affects NK_1 receptors “through a 5-HT_3 receptor-mediated effect” between the 5-HT_3 and NK_1 receptors. *Id.* The literature identifies this internalization as “***a mechanistic explanation of*** the additive and ***synergistic effects*** on the NK_1 receptor antagonism when a combination of netupitant and palonosetron is used in these cells.” *Id*. (emphasis added); *see also* EX1041 (Rojas), 365, 368 (unlike other 5-HT_3 receptor antagonists, palonosetron triggered internalization of 5-HT_3 receptors, affecting the “5-HT3 and NK-1 receptor pathways in a dose- and time-dependent fashion”). These post-critical date publications identify the NK_1-receptor-internalization-property of palonosetron as

a property intrinsic to that prior art 5-HT_3 receptor antagonist. Any alleged additive or synergistic effect on NK_1 receptor antagonism is thus inherent to the obvious combination of therapeutically-effective amounts of palonosetron and an NK_1 receptor antagonist.

199. Because the additive/synergistic effect is an inherent property that naturally results from administering therapeutically effective amounts of palonosetron and an NK_1 receptor antagonist—a combination that MASCC teaches is favorable particularly for palonosetron's additional efficacy for treating delayed emesis—this allegedly unexpected result is merely an inherent property of a prior art or at least an obvious combination.

200. Accordingly, it is my opinion that claim 25 was obvious as a whole over MASCC and Bös.

F. Motivation to Combine

201. By November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the triple antiemetic combination therapy provided in MASCC, using therapeutically effective amounts of the new NK_1 and 5-HT_3 receptor antagonists as claimed.

202. As I explained above, persons having ordinary skill in the art would have had good reason to prophylactically treat patients receiving highly and moderately emetogenic chemotherapy with therapeutically effective amounts of the MASCC triple therapy to provide an antiemetic effect. *See* Section XII.A; EX1013 (MASCC), 22. Above I also explain that a person having ordinary skill in the art would have modified the MASCC triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron. Section XII.A, above; EX1013 (MASCC), 24. Additionally, palonosetron was known to be available in an oral formulation (0.56 mg palonosetron HCl). EX1015 (Aloxi); EX1052 (RxList); EX1053 (DailyMed); EX1054 (DailyMed Archived). The POSA would have been motivated to administer to the patient the oral form of palonosetron HCl as the 5-HT_3 receptor antagonist for ease to both patient and practitioner, as well as for improved patient perception and comfort, as described above.

203. The person having ordinary skill in the art also would have modified the MASCC triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the antiemetic drug combination of MASCC with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the MASCC antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist

netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Section XII.A, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös explained the netupitant is administered orally (administration of oral doses as compared to intravenous has benefits as I described above) (*id.*, 19:2-38) and provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to replace aprepitant with netupitant, and would have had a reasonable expectation of success in doing so.

204. Accordingly, persons having ordinary skill in the art would have had good reason to modify the MASCC triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

G. Reasonable Expectation of Success

205. Persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the MASCC triple active combination therapy with the claimed netupitant and palonosetron therapeutics. As I explained above, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) of MASCC would work in the same manner to achieve a similar (or improved) outcome. Section XII.A, above; EX1013 (MASCC), 23-24.

206. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. MASCC recognized that "Aprepitant is the first of a new class of drugs" and thus envisioned additional members of that class would likely follow, which would likewise be included in the MASCC antiemetic drug combination. *Id.*, 22. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected therapeutically effective amounts of aprepitant and

netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would improve or be similar to the MASCC antiemetic drug combination as compared to the standard therapy (using ondansetron, without NK_1 receptor antagonist).

207. Accordingly, the POSA had good reason to combine MASCC and Bös to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XIII. ['826 PATENT GROUND 3] '826 PATENT CLAIMS 19-23 & 25 WERE OBVIOUS OVER MASCC, BÖS & ALOXI

208. For the reasons discussed in detail below, it is my opinion that each of claims 19-23 and 25 of the '826 patent was obvious as a whole. The obviousness of claims 19-23 and 25 is exemplified by disclosures in the MASCC, Bös & Aloxi references.

209. I have evaluated below whether the combination of MASCC, Bös & Aloxi discloses each and every element of each of claims 19-23 and 25 of the '826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of

success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

210. As a high-level summary, MASCC discloses methods of treating both nausea and vomiting in human subjects in need of such antiemetic treatment during both the acute and the delayed phases of chemotherapy induced nausea and vomiting in response to emetogenic chemotherapy. EX1013 (MASCC), 22. MASCC describes a combination antiemetic therapy administered in response to highly or moderately emetogenic chemotherapy, the prophylactic therapy comprising pre-administration of an NK_1 receptor antagonist in combination with dexamethasone and a 5-HT_3 receptor antagonist. *Id.*, 23. MASCC explains that the addition of an NK_1 receptor antagonist enhanced efficacy as compared to the latter two components alone. *Id.* MASCC specifically describes administering to the subject, prior to chemotherapy, an effective amount of the NK_1 receptor antagonist aprepitant. *Id.* MASCC explains that aprepitant is merely the first of this new class of selective NK_1 receptor antagonists to be employed in this combination. *Id.*, 22. Bös describes netupitant as a new NK_1 receptor antagonist. EX1014 (Bös), 18:42-19:38. It is my opinion that it would have been obvious to a POSA to employ the second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the triple-agent combination disclosed in MASCC.

211. MASCC also advocated for use of palonosetron as the 5-HT_3 receptor antagonist in the combination. EX1013 (MASCC), 24. Aloxi discloses orally administered capsules of palonosetron hydrochloride for treatment of CINV. EX1015 (Aloxi), 1. Aloxi teaches the 0.56 mg palonosetron HCl dose (equivalent to 0.50 mg free base) (*id.* 3) is not inferior to 0.25 mg palonosetron administered intravenously. *Id.*, 4. A POSA would have recognized that the ability to administer the NK_1 receptor antagonist orally was advantageous because:

> At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are ***less costly and more convenient***; for those reasons, they are recommended over intravenous therapy.

EX1018 (Gralla), 2976. The POSA would have understood that oral administration is simpler, less costly, more convenient, and more preferred than intravenous administration. I explained above that Bös discloses netupitant and that the combination of Bös and MASCC disclose claimed features. Section XII.

212. The sections below explain in more detail how MASCC, Bös, and Aloxi disclose each and every element of claims 19-23 and 25. I first analyze independent claim 19 of the challenged ’826 patent. Thereafter, I analyze dependent claims 20-23 and 25.

A. Claim 19

> **19[pre].** A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of

chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising

213. I have reproduced above the preamble of claim 19 of the ’826 patent. I explained above how the combination of MASCC and Bös teaches the preamble. *See* Section XII.A, above. For at least these same reasons, the combination of MASCC, Bös, and Aloxi discloses the subject matter recited in the preamble of claim 19.

19[a]. administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and

214. I have reproduced above the administering step [a] element of claim 19. I explained above how the combination of MASCC and Bös teaches the administering step [a]. *See* Section XII.A, above. For at least these same reasons, the combination of MASCC, Bös, and Aloxi discloses the administering step [a].

19[b]. a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.

215. I have reproduced above the administering step [b] element of claim 19 of the challenged ’826 patent. I explained above how the combination of MASCC and Bös teaches the administering step [a]. *See* Section XII.A, above. For at least these same reasons, the combination of MASCC, Bös, and Aloxi discloses the administering step [a].

216. Furthermore, Aloxi discloses administering to a subject, prior to chemotherapy, a therapeutically effective amount of palonosetron in a

pharmaceutically acceptable salt form. Aloxi teaches its capsules contain 0.56 mg palonosetron HCl (equivalent to 0.50 mg palonosetron free base). EX1015 (Aloxi), 3. Aloxi also describes such doses of palonosetron HCl displayed efficacy for treating emetogenic chemotherapy. *Id.*, 4 (clinical studies). Aloxi teaches the capsules are administered "one hour prior to" administration of "emetogenic chemotherapy." *Id.*, 4.

217. As I explained above (Section XII.A), MASCC describes palonosetron was available for intravenous administration. The POSA also would have recognized the benefits of administering palonosetron orally as an alternative to intravenously (Section XII.A). Because Aloxi's palonosetron HCl is the same free base active ingredient as MASCC's palonosetron, the POSA would have had a reasonable expectation of success in combining the teachings of MASCC, Bös, and Aloxi.

218. The combination of MASCC, Bös, and Aloxi thus teaches all of the elements of claim 19 and rendered the claim obvious as a whole.

B. Claim 20

> **20.** The method of claim 19, comprising orally administering from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof, and from about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically acceptable salt thereof.

219. Claim 20 additionally recites that the netupitant is orally administered in an amount of about 200 to about 400 mg, and that the palonosetron is orally administered in an amount of about 0.25 to about 0.75 mg.

220. As I have previously addressed above, claim 19 was obvious over MASCC, Bös, and Aloxi. Section XIII.A, above. Additionally, as I explained above, orally administering from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof was obvious over MASCC and Bös. Section XII.B, above.

221. Furthermore, Aloxi teaches orally administering 0.56 mg of palonosetron HCl—i.e., within the range of from about 0.25 to about 0.75 mg of palonosetron or a pharmaceutically accept able salt thereof. Aloxi teaches its palonosetron HCl is administered in capsules containing "0.56 mg of palonosetron HCl equivalent to palonosetron 0.5 mg." EX1015 (Aloxi), 3. Aloxi describes the capsules were orally administered to patients receiving emetogenic chemotherapy to prevent CINV. *Id.*, 4.

222. As I describe above (Sections XII.A, XIII.A), a POSA would have had good reason to administer each of the therapeutic agents in an oral form with a reasonable expectation of success. The POSA also would have had good reason to orally administer the Aloxi palonosetron HCl capsules because the dose and

formulation described in Aloxi had been approved by the FDA for its antinausea and antivomiting therapeutic effect. EX1015 (Aloxi), 2.

223. Accordingly, it is my opinion that claim 20 as a whole was also obvious over MASCC, Bös, and Aloxi.

C. Claim 21

> **21.** The method of claim 19, comprising orally administering about 300 mg of netupitant as the free base and about 0.56 mg of palonosetron hydrochloride.

224. Claim 21 additionally recites that the netupitant is orally administered in a dose of about 300 mg as a free base, and about 0.56 mg of palonosetron hydrochloride is orally administered.

225. As I have previously addressed above, claim 19 was obvious over MASCC, Bös, and Aloxi. Section XIII.A, above.

226. Bös explains that it was known to orally administer doses including about 300 mg of NK1 receptor antagonists including netupitant. For example, Bös teaches:

> In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. It is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common

starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization.

227. It would have been routine for a POSA in view of the disclosures of MASCC, Bös, and Aloxi to perform a dose-ranging study to identify a therapeutically effective dose of orally administered netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). MASCC teaches that when determining a therapeutically effective amount of NK_1 receptor antagonist, a randomized study may be used with doses ranging over approximately an order of magnitude to determine what dose "had 'the most favorable benefit:risk profile.'" EX1013 (MASCC), 22. A POSA would have had good reason to implement such a randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile. A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating CINV.

228. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '826 patent. That dose-ranging studies were routinely performed to determine the

therapeutically effective amount is also illustrated by the ’826 patent specification, which explains:

> As used herein, “therapeutically effective amount” refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1001 (’826 patent), 7:55-61. Therefore, the ’826 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant, and in view of MASCC (using therapeutic amounts of the antiemetic drug). Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

229. The ’826 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’826 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug

interaction study (EX1001 (’826 patent), 16:1-36) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1001 (’826 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 16:36-65), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’826 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

230. Aloxi teaches orally administering 0.56 mg of palonosetron HCl. Aloxi teaches its palonosetron HCl is administered in capsules containing “***0.56 mg of palonosetron HCl*** equivalent to palonosetron 0.5 mg.” EX1015 (Aloxi), 3. Aloxi describes the capsules were orally administered to patients receiving emetogenic chemotherapy to prevent CINV. *Id.*, 4. As I described above, the POSA would have had good reason to prophylactically administer its palonosetron in the Aloxi formulation and would have had a reasonable expectation of success in doing so. Section XIII.A, above.

231. Accordingly, it is my opinion that claim 21 as a whole was also obvious over MASCC, Bös, and Aloxi.

D. Claim 22

> **22.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, administering a sub-therapeutic dose of dexamethasone on days one, two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

232. I have reproduced above claim 22 of the challenged '826 patent. I explained above how the combination of MASCC and Bös teaches this claim. *See* Section XII.C, above. For at least these same reasons, the combination of MASCC, Bös, and Aloxi rendered obvious this claim.

233. Furthermore, Aloxi discloses—if the patient is undergoing emetogenic chemotherapy—administering palonosetron on day one. While Aloxi states that its indication is for prevention of CINV for moderately emetogenic chemotherapy (EX1015 (Aloxi), 2), it also suggests administering the Aloxi palonosetron HCl capsules for treatment with cisplatin—a highly emetogenic chemotherapy. EX1015 (Aloxi), 3. Aloxi also instructs that the palonosetron HCl is administered "one hour before the start of chemotherapy" (*id.*, 4), and thus that the palonosetron is administered on day one of the therapeutic regimen.

234. As I explained above (Section XII.A), MASCC describes palonosetron was available for intravenous administration. The POSA also would

have recognized the benefits of administering palonosetron orally as an alternative to intravenously (*id.*, Section XII.A). Because Aloxi's palonosetron HCl is the same free base active ingredient as MASCC's palonosetron, the POSA would have had a reasonable expectation of success in combining the teachings of MASCC, Bös, and Aloxi.

235. The combination of MASCC, Bös, and Aloxi thus teaches all of the elements of claim 22 and rendered the claim obvious as a whole.

E. Claim 23

> **23.** The method of claim 19, further comprising, if said patient is undergoing highly emetogenic chemotherapy, orally administering 12 mg of dexamethasone on day one and 8 mg of dexamethasone on days two, three and four, wherein day one is the day on which netupitant and palonosetron, or pharmaceutically acceptable salts thereof, are administered.

236. I have reproduced above claim 23 of the challenged '826 patent. I explained above how the combination of MASCC and Bös teaches this claim. *See* Section XII.D, above. Additionally, I explained above (Section XIII.D) that Aloxi teaches palonosetron HCl is administered on day one. For at least these reasons, MASCC, Bös, and Aloxi rendered obvious this claim.

237. Accordingly, it is my opinion that claim 23 was obvious as a whole over MASCC, Bös, and Aloxi.

F. Claim 25

> **25.** The method of claim 19, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or

pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK_1 activity.

238. I have reproduced above claim 25 of the challenged ’826 patent. I explained above how the combination of MASCC and Bös teaches this claim. *See* Section XII.E, above. For at least these same reasons, the combination of MASCC, Bös, and Aloxi rendered obvious this claim.

239. Accordingly, it is my opinion that claim 25 was obvious as a whole over MASCC, Bös, and Aloxi.

G. Motivation to Combine

240. As I explained above (Sections XI.A, XI.E, XII.A, XII.F), persons having ordinary skill in the art would have had good reason to modify the MASCC triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös’ NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

241. The persons having ordinary skill in the art also would have been motivated to administer palonosetron in an oral formulation. Aloxi describes an FDA-approved oral capsule of palonosetron HCl that was shown to provide antiemetic effect when administered to patients receiving emetogenic chemotherapy. EX1015 (Aloxi), 2-4. Thus, the POSA would have had good reason to use the Aloxi capsule of palonosetron HCl for its administration of palonosetron.

H. Reasonable Expectation of Success

242. As I explained above (Sections XI.A, XI.F, XII.A, XII.G), persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome. Similarly, I explained above that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. Sections XI.A, XI.F, XII.A, XII.G, above.

243. The POSA also would have had a reasonable expectation of success in using the palonosetron HCl capsules of Aloxi to administer the MASCC palonosetron. Aloxi explains the orally administered palonosetron HCl capsules were as efficacious as the previously-FDA-approved intravenous formulation. EX1015 (Aloxi), 4 (non-inferiority studies). Additionally, Aloxi provides clinical studies showing the 0.56 mg palonosetron HCl capsules were therapeutically effective in treating CINV, leading to FDA approval for prophylaxis with emetogenic chemotherapy. *Id.*, 2, 4. Therefore, the POSA would have had a

reasonable expectation of success that Aloxi's palonosetron HCl capsules would treat CINV when incorporated into the MASCC study.

244. Accordingly, the POSA had good reason to combine MASCC, Bös, and Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XIV. ['826 PATENT GROUND 4] '826 PATENT CLAIMS 1-3, 8-10, 15-18, AND 24 WERE OBVIOUS OVER HERRSTEDT, HOFFMANN & HARGREAVES

245. For the reasons discussed in detail below, it is my opinion that each of claims 1-3, 8-10, 15-18, and 24 of the '826 patent was obvious as a whole. The obviousness of claims 1-3, 8-10, 15-18, and 24 is exemplified by disclosures in the Herrstedt, Hoffmann, and Hargreaves references.

246. I have evaluated below whether the combination of Herrstedt, Hoffmann, and Hargreaves discloses each and every element of each of claims 1-3, 8-10, 15-18, and 24 of the '826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

247. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010

(Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt discloses administering to the patient on day one a therapeutically effective amount of a 5-HT_3 receptor antagonist (EX1010 (Herrstedt), 146) and teaches that palonosetron is a new 5-HT_3 receptor antagonist (*Id.*). Herrstedt also discloses administering to the patient on day one a first dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146. Further, Herrstedt describes the above steps are effective for treating both nausea and vomiting to a greater extent during the 5-day period as compared to a combination of just the 5-HT_3 receptor antagonist and dexamethasone. *Id.*, 146-147. Hoffmann describes netupitant as a new NK_1 receptor antagonist. EX1011 (Hoffmann), Abstract, 1364. It is my opinion that it would have been obvious to a POSA to employ the second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1

receptor antagonist (aprepitant) in the triple-agent combination disclosed in Herrstedt.

248. Hargreaves explains NK_1 receptor occupancy of greater than 75% is associated with therapeutic effectiveness. EX1012 (Hargreaves), Abstract, 23, Fig. 6B. Hargreaves also teaches to measure NK_1 receptor occupancy in the striatum. As I explain further below, a POSA would have understood the therapeutically effective dose of netupitant would likely occupy at least 75% of NK_1 receptors in the striatum after prophylactic administration. Section XIV.A. The skilled artisan would have reasonably expected that a prophylactically administered therapeutically effective dose of netupitant (e.g., 300 mg) would naturally result in very high occupancy of NK_1 receptors in the striatum (e.g., greater than 70%) and that due to netupitant's long half-life, it is a natural result that there would still be high occupancy of the striatum NK_1 receptors at 72 hours.

249. The sections below explain in more detail how Herrstedt, Hoffmann, and Hargreaves disclose each and every element of claims 1-3, 8-10, 15-18, and 24. I first analyze independent claim 1 of the challenged '826 patent. Thereafter, I analyze dependent claims 2-3, 8-10, 15-18, and 24.

A. Claim 1

1[pre]. A method of treating both nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

250. I have reproduced above the preamble of claim 1 of the ’826 patent. Herrstedt teaches a “method of treating both nausea and vomiting for five consecutive days in a patient in need thereof” as disclosed in the preamble of claim 1. For example, Herrstedt teaches methods for prophylactically treating “[c]hemotherapy-induced ***nausea and vomiting***” in a patient. EX1010 (Herrstedt), 143. Herrstedt describes its primary therapeutic endpoint was no emesis for five consecutive days following administration of the chemotherapeutic, cisplatin (i.e., five days “postcisplatin”). *Id.*, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1–5 postcisplatin’, was the primary end-point in all studies.”). Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in the preamble of claim 1.

> **1(a)[1].** a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof,

251. I have reproduced above the administering step (a)[1] element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the administering step of claim 1(a)[1].

252. Herrstedt expressly discloses multiple studies for treatment of highly-emetogenic chemotherapy in patients with a triple-drug combination administered to patients on day one including an NK_1 receptor antagonist (aprepitant). EX1010 (Herrstedt), 146 (“Two of the HEC studies used an identical design…ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus

aprepitant days 2-3."). Herrstedt describes benefits to patients receiving the triple-drug antiemetic combination (including NK_1-receptor antagonist) administered on day one. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm."); *see also* EX1016 (Herrington), Abstract, 2084 (NK_1 receptor antagonist administered on Day 1 before chemotharpy provided antiemetic effect).

253. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Hoffmann not only discloses netupitant as a selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant as an "excellent" alternative to aprepitant. For example, in Hoffmann:

> The evaluation of this [NK_1 receptor antagonist] class is briefly outlined, leading to the identification of netupitant 21[, one of] two new proprietary chemical entities with high affinity and excellent CNS penetration.

EX1011 (Hoffmann), Abstract.

254. It is my opinion that a POSA would have understood Hoffmann as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant)

with the second generation NK_1 receptor antagonist of Hoffmann (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

255. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in the claim element 1(a)[1].

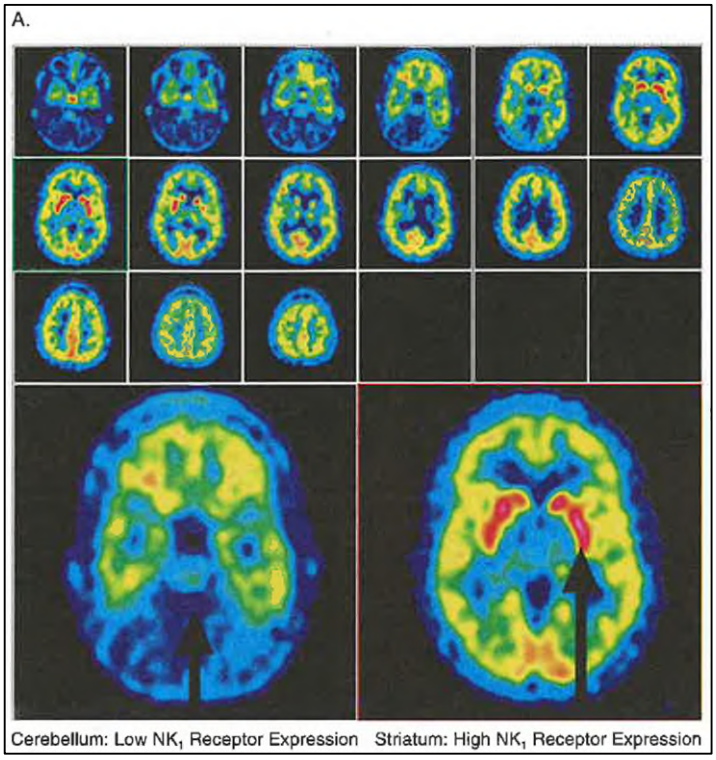
> **1(a)[2].** In a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK) receptors in the striatum seventy-two hours after said administration;

256. I have reproduced above the therapeutically effective amount (a)[2] element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the therapeutically effective amount of claim 1(a)[2].

257. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Hoffmann describes netupitant is administered orally. EX1011 (Hoffmann), 1364 ("Animals were orally pretreated (2 h) with the test compound followed by central

injection (icv) of the NK_1-selective receptor agonist GR73632. Excellent oral activity was observed…for netupitant."). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. Indeed, netupitant was praised precisely because of its ability to penetrate the CNS. See, e.g., EX1011 (Hoffmann), Abstract ("excellent CNS penetration"). A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

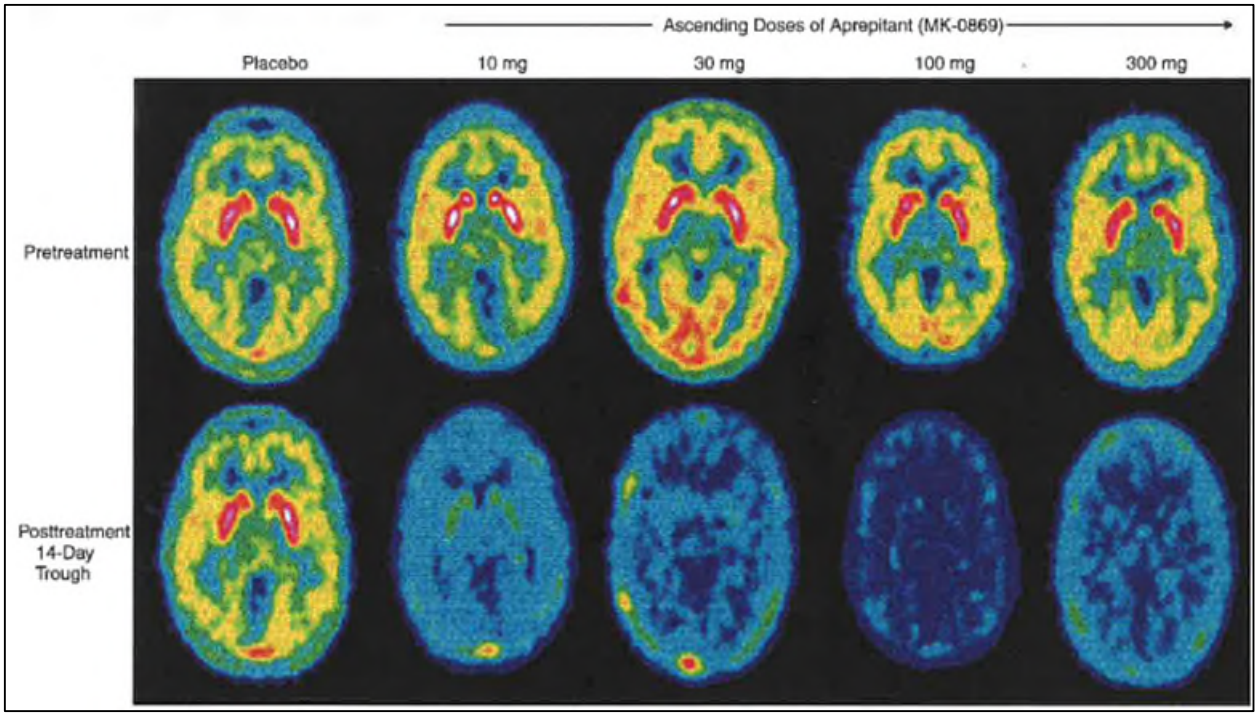
258. Hargreaves teaches that, to be considered a therapeutically effective amount, an NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).

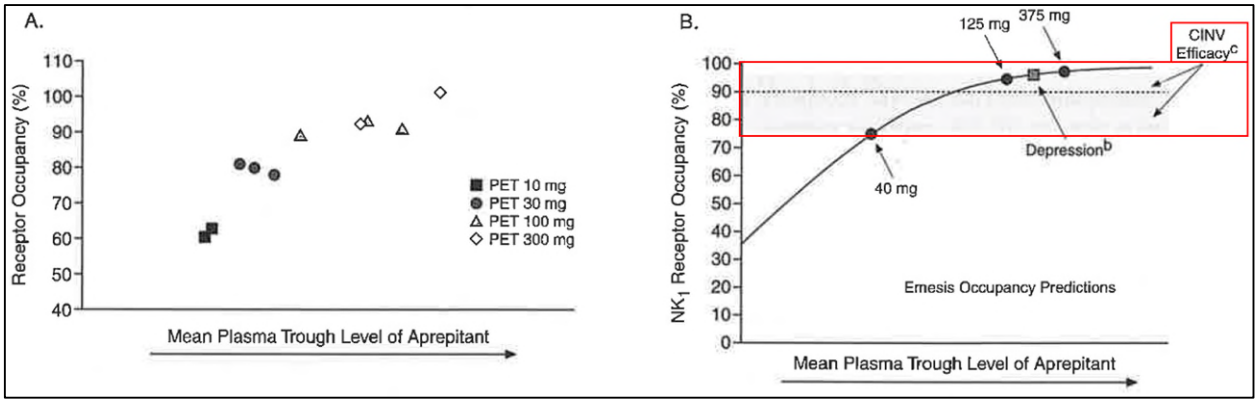


259. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS

(Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



EX1012 (Hargreaves) Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the therapeutically effective amount of claim 1(a)[2]. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum seventy-two hours (i.e., 3 days into the 5-day course of treatment) after administration would be very likely to be efficacious for treating CINV.

260. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Sections V.C-V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; sections V.C-V.D, above. The '826 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration." EX1001 ('826 patent), 4:37-

51. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

261. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(a)[2].

> **1(b).** b) administering to said patient on day one a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof; and;

262. I have reproduced above the administering step (b) element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the administering step of claim 1(b).

263. Herrstedt teaches or suggests administering a therapeutically effective amount of palonosetron to said patient on day one. For example, Herrstedt identifies palonosetron as a favorable 5-HT_3 receptor antagonist for treating emesis. EX1010 (Herrstedt), 146. Herrstedt specifically teaches palonosetron differed from other 5-HT_3 receptor antagonists because it showed beneficial properties "in the treatment of delayed emesis from MEC" and also had an order of magnitude increase in half-life as compared to the 5-HT_3 receptor antagonist ondansetron. *Id.*, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours); *see also id.*, 146 ("in the MEC studies some of the evaluable parameters ***significantly favoured palonosetron***."). Herrstedt further describes palonosetron as a suitable substitution for ondansetron for treating emesis, stating:

"Palonosetron has been compared to ondansetron and dolasetron in three randomized, double-blind trials" and each "demonstrated that palonosetron was not inferior to dolasetron and ondansetron." *Id.*, 146. Thus, a POSA would have had good reason to employ a therapeutically effective amount of the "significantly favoured" palonosetron as the 5-HT_3 receptor antagonist to said patient. Furthermore, the POSA would have had a reasonable expectation of success in making such a substitution because both palonosetron and ondansetron worked through an identical mechanism (i.e., 5-HT_3 receptor antagonism) to achieve the same therapeutic result (i.e., anti-emesis).

264. Herrstedt also expressly disclosed the therapeutically effective amount of 5-HT_3 receptor antagonist should be administered to said patient on day one. For example, Herrstedt explains that a therapeutically effective amount of the 5-HT_3 receptor antagonist is administered to the patient on day one in both the standard study (5-HT_3 receptor antagonist and dexamethasone) and the study evaluating triple therapy adding NK_1 receptor antagonist:

> Two of the HEC studies used an identical design comparing ***ondansetron***, dexamethasone and placebo ***day 1*** followed by dexamethasone plus placebo days 2-4 with ***ondansetron***, dexamethasone and aprepitant ***day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3.

EX1010 (Herrstedt), 146. Herrstedt explains that latter studies copied this dosing of 5-HT_3 receptor antagonist on day 1 (prior to chemotherapy). *Id.* ("The most recently published HEC study used the same design, except that ondansetron was [also] included in the control arm for delayed protection days 2-4.").

265. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(b).

> **1(c).** administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant,

266. I have reproduced above the administering step (c) element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the administering step of claim 1(c).

267. Before looking to evaluate whether the prior art discloses this limitation, I look to the specification of the '826 patent exclusively to understand what the claim means when it says a first dose of dexamethasone is "ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant." For example, the specification admits that a 20 mg dose of dexamethasone was known in the field as the minimum day-one therapeutically effective dose for treating CINV:

> The ***minimum effective dose of dexamethasone***, when used to treat

> CINV induced by highly emetogenic chemotherapy, has been demonstrated to be ***20 mg***. administered orally or by injection ***on day one***, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the ***minimum effective dose of dexamethasone*** is ***20 mg***. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1001 ('826 patent), 7:62-8:4 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). As defined in the patent specification, the claim term "dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone" encompasses any day one dose of less than 20 mg. The prior art routinely described this same 20 mg dose as the standard day one dose for treating emetogenic chemotherapy. *See, e.g.*, EX1010 (Herrstedt), 145 ("single intravenous dose of 20 mg" for highly emetogenic chemotherapy); EX1025 (Chawla), 2292 (standard therapy regimen included oral dexamethasone 20 mg on Day 1); EX1013 (MASCC), Table 3 (20 mg dexamethasone for patients not receiving aprepitant).

268. Understanding the claim term as illustrated in the patent specification, Herrstedt discloses administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when

administered in combination with the NK_1 receptor antagonist. For example, Herrstedt teaches administering a single, sub-20 mg day one dose of dexamethasone for the treatment of moderately emetogenic chemotherapy, a treatment that leads to CINV. EX1010 (Herrstedt), 145-147. In contrast to the standard 20 mg day one dose, Herrstedt teaches that the day one dexamethasone should be administered in a reduced amount—about 25% to 50% less than the 20 mg (minimally effective) standard dose discussed above. *Id.* Such reduced amount was, by itself, ineffective against CINV, but when administered with the combination of therapeutics (including 5-HT_3 and NK_1 receptor antagonists), the reduced amount of dexamethasone was effective against CINV.

269. Herrstedt explains that due to metabolic interactions of corticosteroids (e.g., dexamethasone or methylprednisolone) and the NK_1 receptor antagonist (aprepitant), the corticosteroid should be administered in a lower-than-typically-therapeutic dose when treatment includes the NK_1 receptor antagonist. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone,

when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

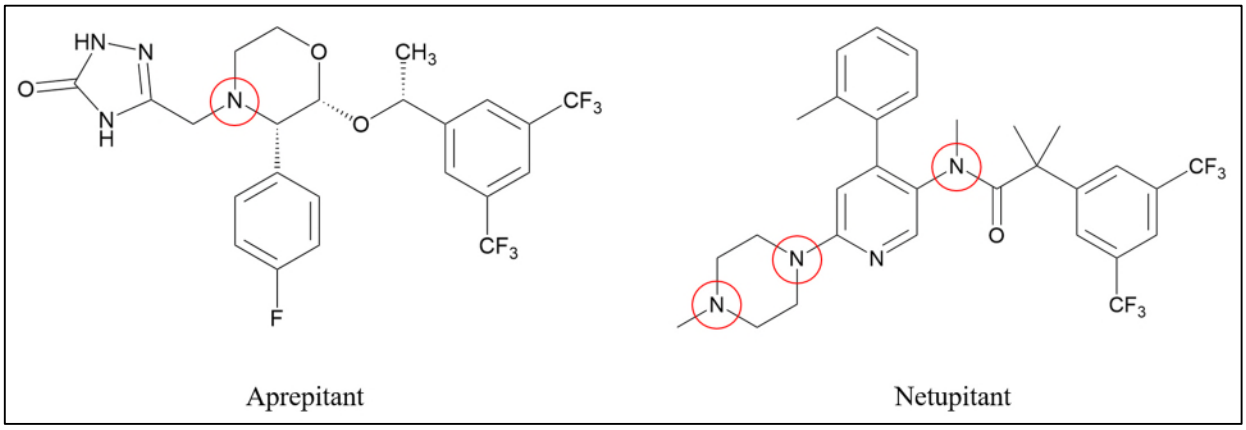
> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Therefore Herrstedt suggests the dose of dexamethasone—when administered with NK_1 receptor antagonist—should be a reduced dose which, by itself would be ineffective against CINV, but when administered in combination with NK_1 receptor antagonist is effective against CINV because it provides the same total exposure of dexamethasone AUC. Thus, Herrstedt describes administering to the patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with the NK_1 receptor antagonist.

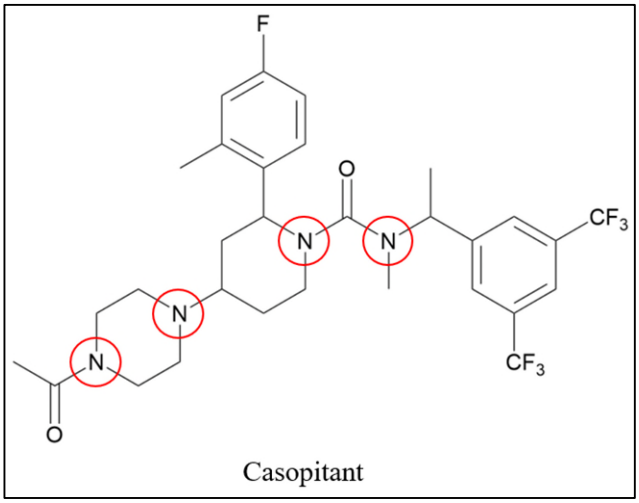
270. Based on the experience with aprepitant, a POSA would have had good reason to determine the dexamethasone AUC when administered with netupitant compared to administration of dexamethasone alone. Evaluating such drug-drug interactions was well-known and routine in the field. EX1049 (Zhou), 318 ("Drug-drug interactions remain an important issue in clinical practice and drug development"). Evaluating such drug-drug interactions (e.g., NK_1-receptor-

antagonist-induced dexamethasone potentiation) was a fundamental prerequisite when administering a combination therapy, such as the combination antiemetic therapy at issue. EX1010 (Herrstedt), 147 ("Risk of drug-drug interactions with the use of anti-emetics" due to "concomitant treatment with supportive care drugs" should be evaluated). Understanding the interaction of therapeutic agents with their metabolism provided necessary insight for evaluating drug-drug interactions. EX1044 (Schoenwald), 86 ("By understanding which metabolic steps may be susceptible to induction or inhibition by other drugs, specific *in vitro* or clinical drug interaction studies may be conducted to determine the potential risks of drug-drug interactions."). Among other interactions, a POSA would have had good reason to measure the impact of netupitant administration on the cytochrome P450 (CYP) 3A4 ("CYP3A4") enzyme-mediated metabolism of dexamethasone. This particular cytochrome P450 was known to "metaboliz[e] more than 50% of [] clinically used drugs." EX1049 (Zhou), 310. In addition to metabolizing "more than 50% [of] therapeutic drugs" CYP3A4 was known to have "very broad" substrate specificity "with an extremely large number of structurally divergent chemicals being metabolized." *Id.*, 311. In other words, it was well-known CYP3A4 had high "ligand promiscuity" for metabolism and a high likelihood of being involved in the metabolism of a given therapeutic agent. *Id.* Additionally, CYP3A4 was known to be inhibited by a variety of substrates sharing common

structural features with aprepitant and netupitant. For example, drugs known to inactivate CYP3A4 "often possess a number of structural similarities such as a tertiary amine function[.]" EX1049 (Zhou), 314. Both aprepitant and netupitant had such tertiary amine function, as shown in the below figure (red circles annotating tertiary amines).



It was known that aprepitant was a substrate and moderate inhibitor of CYP3A4, leading to increased AUC exposure of dexamethasone. EX1010 (Herrstedt), 147; Sections IX.A, IX.E, above (50% increase). Likewise, it was known that the NK_1 receptor antagonist casopitant—structurally similar to netupitant—was also a substrate and weak-to-moderate inhibitor of CYP3A4, requiring "a reduction in dexamethasone dose of 40-50%, when repeat-dose oral dexamethasone is to be co-administered with oral casopitant." EX1042 (Ruhlmann), 377-378; *see also* the below figure where I provide the structure with annotations of tertiary amines.



Casopitant

Thus, a POSA would have expected netupitant to act similarly as substrate and inhibitor of CYP3A4. Accordingly, it would have been obvious and routine to a POSA in view of Herrstedt, Hoffmann, and Hargreaves to measure the impact of netupitant co-administration on dexamethasone AUC and to lower the dexamethasone dose accordingly. Because the patent defines the sub-therapeutic dose of dexamethasone to encompass any day one dose below the standard 20 mg dose, any actual reduction from the standard day one dose satisfies the claims.

271. Having good reason to co-administer netupitant with dexamethasone (as discussed above), the reduced metabolism of dexamethasone when co-administered with netupitant is a property that necessarily and naturally flows from the combination. Accordingly, a POSA performing routine metabolism studies on the combination therapy would reasonably expect to measure the increased dexamethasone AUC and to reduce the dexamethasone dose below the 20 mg

(minimally effective) standard dose, which dose reduction the patent itself admits satisfies the claim.

272. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(c).

> **1(d).** wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

273. I have reproduced above the decreased dexamethasone dose (d) element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the decreased dexamethasone dose of claim 1(d).

274. As I explained above for element 1(c), Herrstedt explains the day one dose of dexamethasone should be administered in a reduced amount—including by about 50 to 70%—compared to the 20 mg dose. As I explained above, it was known NK_1 receptor antagonists increased the AUC concentration of dexamethasone, and Herrstedt teaches a corresponding reduction of the dexamethasone dose. For example, Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral***

> ***dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Herrstedt thus teaches reducing the day one dose of oral dexamethasone, when administered with an NK_1 receptor antagonist, by about 50% of the minimum effective dose when administered alone to achieve the same effective AUC concentration. Furthermore, Herrstedt discloses that administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study," each of which discloses the first dose of dexamethasone comprises 12 mg (60% of the 20 mg minimum effective dose), confirming that Herrstedt teaches reducing the day one dose. EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)); EX1039 (Poli-Bigelli), Abstract ("oral dexamethasone 12 mg on Day 1"); EX1037 (Hesketh), 4113 ("oral dexamethasone 12 mg on day 1"). Accordingly, Herrstedt discloses element 1(d). *See also* Sections IX.A, IX.E, above (prior art taught to reduce dexamethasone when administered with NK_1 receptor antagonists).

275. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(d).

1(e). steps a, b and (c) are effective to treat both nausea and vomiting during the period defined by days one through five; and

276. I have reproduced above the efficacy (e) element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the efficacy element of claim 1(e).

277. Herrstedt teaches or suggests each of steps (a), (b), and (c) of claim 1, as I detailed above, with Hoffmann disclosing netupitant. Herrstedt teaches that the steps are effective to treat both nausea and vomiting over a treatment period defined by days one through five:

> Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. ***Complete response, defined as "no emesis and no rescue therapy on days 1-5 postcisplatin," was the primary end-point in all studies***. Two of the HEC studies used…ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, a complete response of 72.7% in the aprepitant arm versus 53.3% in the control arm was seen[.]

EX1010 (Herrstedt), 146. Herrstedt describes the triple therapy combination (5-HT_3 receptor antagonist, dexamethasone, and NK_1 receptor antagonist) is recommended "for ***prevention of acute and delayed nausea and vomiting***." *Id.*, 148 & Table 4 (MASCC guidelines). The acute time period (0-24 hours) and delayed time period (24-120 hours) encompasses days one through five. *Id.*, 143.

278. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(e).

> **1(f).** steps (a), (b) and (c) are effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five than steps (b) and (c) alone.

279. I have reproduced above the efficacy (f) element of claim 1. It is my opinion that the combination of Herrstedt, Hoffmann, and Hargreaves teaches or suggests the efficacy of claim 1(f).

280. As described above, the combination of Herrstedt, Hoffmann, and Hargreaves teach the triple therapy of steps (a) (administering NK_1 receptor antagonist netupitant), (b) (administering 5-HT_3 receptor antagonist palonosetron), and (c) (administering dexamethasone) is a more effective combination than the standard therapy (administering 5-HT_3 receptor antagonist with dexamethasone). EX1010 (Herrstedt), 146 (adding NK_1 receptor antagonist aprepitant improved response rates in all studies). Claim element 1(f) further requires that the triple therapy is "effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five" than the standard therapy (5-HT_3 receptor antagonist with dexamethasone). In other words, this claim element is directed at showing that administering NK_1 receptor antagonist netupitant improves treatment of both nausea and vomiting during the period defined by days one through five (i.e., the combined acute and delayed phases).

281. Herrstedt explicitly teaches improved effectiveness to treat both nausea and vomiting with the triple therapy (NK_1 receptor antagonist, 5-HT3 receptor antagonist, and corticosteroid) as compared to the corresponding combination without the NK_1 receptor antagonist. For example:

> Complete response, defined as "no emesis and no rescue therapy on days 1-5 postcisplatin," was the primary end-point in all studies. Two of the HEC studies used an identical design comparing ***ondansetron [5-HT3 receptor antagonist], dexamethasone [corticosteroid], and placebo*** day 1 followed by dexamethasone plus placebo days 2-4 with ***ondansetron, dexamethasone and aprepitant [NK_1 receptor antagonist]*** day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, ***a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen***, and in the Poli-Bigelli study complete response rates were 62.7% versus 43.3%. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2-4. Again a ***statistical[] benefit favouring aprepitant was seen***, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.

EX1010 (Herrstedt), 146 (parentheticals omitted). The POSA would have understood that the addition of NK_1 receptor antagonist increased overall efficacy of the therapy. Herrstedt explains the triple therapy was recommended as the new and improved standard for treating highly emetogenic chemotherapy because it facilitated "prevention of ***acute and delayed nausea and vomiting***." EX1010

(Herrstedt), 148 & Table 4 (MASCC recommendations). Because each of the drugs in the combination targets a different mechanism providing relief for a patient suffering from nausea and vomiting, a POSA would have had good reason to combine the medications with a reasonable expectation of success in further improving both nausea and vomiting following CINV during both the acute and delayed period (i.e., during the period defined by days one through five).

282. Accordingly, the combination of Herrstedt, Hoffmann, and Hargreaves discloses the subject matter recited in claim element 1(f).

283. The combination of Herrstedt, Hoffmann, and Hargreaves thus teaches all of the elements of claim 1 and rendered the claim obvious as a whole.

B. Claim 2

> **2.** The method of claim 1, further comprising: d) administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

284. Claim 2 additionally recites that the method is further comprising: (d) administering to said patient, on days two, three and four, a second dose (i.e., having a different strength from day one) of dexamethasone which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said

second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

285. As I have previously addressed above, claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

286. Herrstedt describes its method further comprises administering to said patient, on days two, three, and four, a second dose (i.e., having a different strength from day one) of dexamethasone. Herrstedt identifies several studies having such dosing:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, dexamethasone and aprepitant day 1 followed by ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published HEC study used ***the same design***, except that ondansetron was included in the control arm for delayed protection days 2–4.

EX1010 (Herrstedt), 146. *See also* Section XIV.A, above (routine protocol to dose dexamethasone on subsequent days).

287. Herrstedt suggests the days 2-4 doses of dexamethasone are ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with: (a) administering an NK_1 receptor antagonist and (b) administering a 5-HT_3 receptor antagonist. Herrstedt teaches that a lower dose of corticosteroids, such as

dexamethasone, should be administered when concomitantly administered with an NK_1 receptor antagonist due to resulting increase of AUC exposure. EX1010 (Herrstedt), 147-148; *see also* Section IX.E, above. Thus, when the lower dose of dexamethasone is administered alone against HEC-induced vomiting (i.e., in absence of NK_1 receptor antagonist) it is ineffective against vomiting, but when administered in combination with the NK_1 receptor antagonist and 5-HT_3 receptor antagonist, the lower dose is effective in increasing the efficacy of the combination treatment. *See also* Section XIV.A, above (known CYP3A4 metabolism interaction and corresponding decrease of dose of dexamethasone).

288. Herrstedt also suggests said second dose (i.e., having a different strength from day one) comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting. EX1010 (Herrstedt), 146-147. Herrstedt teaches when corticosteroid (e.g., methylprednisolone) is orally administered with NK_1 receptor antagonist (aprepitant), the dose should be reduced "by 50% to obtain the same exposure." EX1010 (Herrstedt), 147. This is an amount which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with NK_1 and 5-HT_3 receptor antagonists. Herrstedt explains dexamethasone and methylprednisolone are both sensitive to CYP3A4 in the same manner, thus a 50% reduction should be applied to both. EX1010 (Herrstedt), 147. I explained above

that the NK_1 receptor antagonist doubled the dexamethasone AUC exposure, providing good reason to correspondingly halve the dexamethasone dose. *See* Sections IX.E, XIV.A, above; EX1010 (Herrstedt), 147. As I explained above, a POSA would have expected similar increase in dexamethasone AUC exposure following administration of netupitant. *See* Section XIV.A, above. Furthermore, Herrstedt discloses that administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study," each of which discloses the subsequent doses of dexamethasone comprise 8 mg (50% of the 16 mg minimum effective dose (Section XIV.A, above; EX1001 ('826 patent), 7:62-8:4 ("The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, ***has been demonstrated to be***…***sixteen mg.*** administered orally or by injection ***on days two, three and four***") (citing EX1019 (Jordan)))), confirming that Herrstedt teaches reducing the day one dose. EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)); EX1039 (Poli-Bigelli), Abstract ("oral dexamethasone ***8 mg once daily on Days 2-3***; and oral dexamethasone ***8 mg on Day 4***"); EX1037 (Hesketh), 4113 (similar). Herrstedt also teaches an effective amount of NK_1 receptor antagonist is present in the patient in subsequent days. For example, when aprepitant is used as the NK_1 receptor antagonist, it is dosed on days 2-3 (EX1010 (Herrstedt), 146), and it was known netupitant had increased receptor affinity and increased half-life (EX1014 (Bös), 19:3-10 (24-30 hours)).

289. Accordingly, the POSA would have good reason to administer doses of dexamethasone on days two, three, and four in a reduced amount to account for increased AUC exposure based on the continued presence of the NK_1 receptor antagonist. Because the NK_1 receptor antagonist increased dexamethasone AUC, a POSA would have reduced the dexamethasone dose by about 50% to obtain the same total AUC concentration. This reduced amount (50% of the minimally effective dose) of dexamethasone would have been ineffective for antiemetic effect when administered as a monotherapy, but would have been effective when combined with NK_1 receptor antagonists due to the increased AUC concentration.

290. Accordingly, it is my opinion that claim 2 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

C. Claim 3

> **3.** The method of claim 1 or 2, wherein said netupitant occupies at least 80% of NK receptors in the striatum seventy-two hours after said administration.

291. Claim 3 additionally recites that the netupitant occupies at least 80% of NK receptors in the striatum seventy-two hours after said administration.

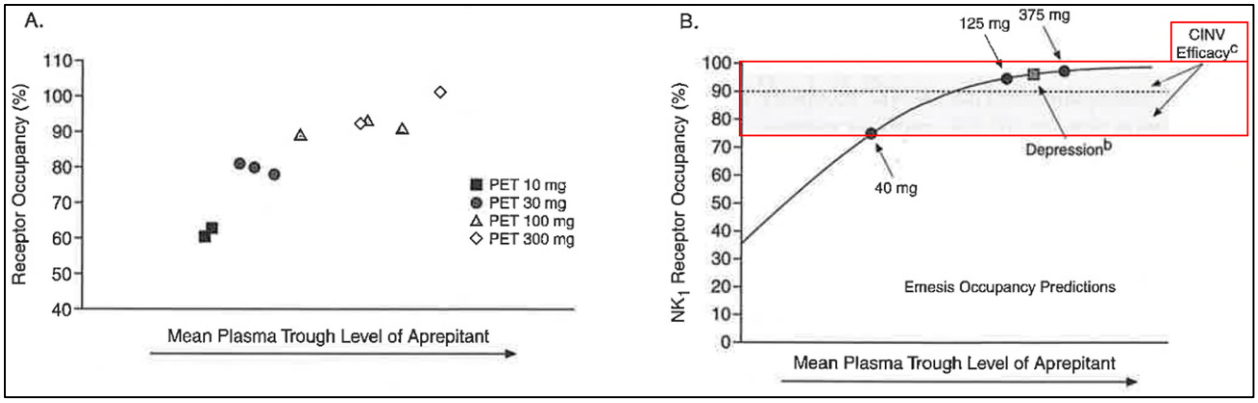
292. I have previously addressed above that each of claims 1 and 2 were obvious over Herrstedt, Hoffmann, and Hargreaves.

293. Hargreaves discloses that there is a direct relationship between occupancy of NK_1 receptors in the striatum and antiemetic effects for patients

suffering from chemotherapy-induced nausea and vomiting, and that clinically effective doses of NK_1 receptor antagonists occupy at least 75-80% of NK receptors in the striatum of patients. Hargreaves discloses:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas ***the occupancy of ≥ 90% of NK_1 receptors*** requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of ***emesis blocked ≥ 90% of NK_1 receptors*** in the CNS (Figure 6B), whereas the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B).

EX1012 (Hargreaves), 23. Thus, Hargreaves teaches the benefits of the NK_1 receptor antagonist occupying high levels of NK receptors in the striatum (e.g., greater than 90%). Reproduced below is an annotated version of Hargreaves Fig. 6.



Notably, Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy is present in a grayed-out region beginning at approximately 75% of NK_1 receptor occupancy. Thus, Hargreaves explicitly describes that a therapeutically effective amount of an NK_1 receptor antagonist is one which occupies high levels of NK_1 receptors (e.g., greater than 75% and preferably greater than 90%) in the striatum.

294. As described above (Section XIV.A), it would have been obvious in view of Hargreaves that a therapeutically effective dose of prophylactically administered netupitant occupies at least 70% of NK_1 receptors in the striatum after administration. As I describe herein, a skilled artisan would have found it obvious to administer netupitant in a therapeutically effective dose (Section XIV.A), and because of netupitant's long half-life, it is a natural result that the prophylactic administration of said therapeutically effective dose maintains at least 70% NK_1 receptor occupancy at 72 hours. The "at least 80%" occupancy limitation is substantially similar to the "at least 75%" occupancy threshold that Hargreaves taught naturally accompanied administration of a therapeutically effective amount

of an NK_1 receptor antagonist for the treatment of emesis. EX1012 (Hargreaves), 23 & Fig. 6. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the ’515 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the “at least 80%” occupancy limitation. For example, the examiner stated that netupitant occupying at least 80% of a patient’s striatum NK_1 receptors was an inherent feature of a therapeutically effective dose of netupitant. *See* Section V.C, above. The examiner also stated that netupitant occupying at least 70% of a patient’s striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant during prosecution of the application that issued as the ’297 patent. EX1008, 120; Section V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See*, *e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner’s position. EX1008, 155; Section V.D, above. The ’826 patent specification reports this is a characteristic of netupitant itself: “netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after

administration." EX1001 ('826 patent), 4:37-51. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

295. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 90% (at least 80%) of NK_1 receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

296. Accordingly, it is my opinion that claim 3 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

D. Claim 8

> **8.** The method of claim 1, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

297. Claim 8 additionally recites that the therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

298. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves. As described above, the prior art routinely described the 20 mg dose as the standard day one dose for treating emetogenic chemotherapy. *See, e.g.*, EX1010 (Herrstedt), 145 ("single

intravenous dose of 20 mg" for highly emetogenic chemotherapy); *see also* EX1025 (Chawla), 2292 (standard therapy regimen included oral dexamethasone 20 mg on Day 1); EX1013 (MASCC), Table 3 (20 mg dexamethasone for patients not receiving aprepitant); Section XIV.A, above.

299. The '826 patent defines that the minimally effective day-one dose of dexamethasone when administered alone was 20 mg. The '826 patent specification admits this was recognized in the field prior to the critical date. The '826 patent states:

> ***The minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, ***has been demonstrated to be 20 mg***. administered orally or by injection ***on day one***, and sixteen mg. administered orally or by injection on days two, three and four. When used to treat CINV induced by moderately emetogenic chemotherapy, ***the minimum effective dose of dexamethasone is 20 mg.*** administered orally or by injection ***on day one***, and zero mg. on days two, three and four.

EX1001 ('826 patent), 7:62-8:4 (citation omitted) (citing EX1019 (Jordan)). Thus, a POSA would have understood that—by definition—the therapeutically minimum effective dose of dexamethasone when administered alone on day one comprises 20 mg of dexamethasone. Herrstedt discloses this dose. EX1010 (Herrstedt), 145 ("In patients receiving cisplatin-based, highly emetogenic chemotherapy (HEC), a

single intravenous dose [of dexamethasone] of 20 mg is superior to lower doses….").

300. Accordingly, it is my opinion that claim 8 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

E. Claim 9

> **9.** The method of claim 1, wherein only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.

301. Claim 9 additionally recites that only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.

302. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

303. Herrstedt discloses only one dose of the 5-HT_3 receptor antagonist (e.g., palonosetron, ondansetron) is administered during the five days. Herrstedt explains:

> Complete response, defined as 'no emesis and no rescue therapy on ***days 1–5 postcisplatin***', was the primary end-point in all studies. Two of the HEC studies used an identical design comparing ***ondansetron***, dexamethasone and placebo ***day 1*** followed by dexamethasone plus placebo days 2–4 with ***ondansetron***, dexamethasone and aprepitant ***day 1*** followed by dexamethasone days 2–4 plus aprepitant days 2–3.

EX1010 (Herrstedt), 146. In other words, the 5-HT_3 receptor antagonist ondansetron was administered only on day one (i.e., there was only one dose of the

5-HT_3 receptor antagonist during the five days). Herrstedt summarizes that the field had embraced administering the 5-HT_3 receptor antagonist in a single dose across the five day period, and suggests that palonosetron should be used as the 5-HT_3 receptor antagonist at least in part because it already also treated delayed emesis:

> Ondansetron and granisetron were initially developed as 8 mg t.i.d. and 3 mg plus up to two additional doses within the first 24 hr after chemotherapy, respectively. ***Today, all these agents are primarily used as a single oral or intravenous dose*** (ondansetron can be given twice daily in patients receiving MEC). Originally ondansetron and granisetron were prescribed for up to 5 days after chemotherapy, but it is now recognized that the 5-HT3-receptor antagonists are primarily effective in the prophylaxis of acute emesis with limited or no efficacy in delayed emesis. ***Palonosetron might be an exception and it has been approved by the Food and Drug Administration*** (but not by the European Medicines Agency) ***in the treatment of delayed emesis*** from MEC.

Id., 145-146.

304. Furthermore, the POSA would have understood that the increased half-life of palonosetron indicated that the single dose of palonosetron on day 1 of therapy (prior to chemotherapy) would be sufficient to confer the delayed emesis benefit provided by palonosetron. Herrstedt describes that palonosetron has an ***order of magnitude*** greater half-life as compared to ondansetron. *Id.*, Table 3

(below).

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

Therefore, the POSA would have had good reason to prophylactically administer only one dose of palonosetron or a pharmaceutically acceptable salt thereof during the five day treatment period.

305. Accordingly, it is my opinion that claim 9 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

F. Claim 10

> **10.** The method of claim 1, wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

306. Claim 10 additionally recites that the therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

307. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

308. Herrstedt discloses that the clinical dose of palonosetron is within the range of about 0.25 to about 0.75 mg based on the weight of the free base.

Herrstedt discloses, in Table 3, that it was known in the art to administer palonosetron in a 0.25 mg intravenous dose.

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

EX1010 (Herrstedt), Table 3. Thus, Herrstedt explicitly discloses administration of palonosetron in a therapeutically effective amount of 0.25 mg, which is within the claimed range of from about 0.25 to about 0.75 mg based on the weight of the free base.

309. Accordingly, it is my opinion that claim 10 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

G. Claim 15

> **15.** The method of claim 1, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

310. Claim 15 additionally recites that the nausea and vomiting is chemotherapy induced nausea and vomiting, radiation therapy induced nausea and vomiting, ***or*** post-operative nausea and vomiting.

311. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

312. Herrstedt describes its combination therapy is used as a prophylactic to treat nausea and vomiting that is chemotherapy induced nausea and vomiting (CINV). Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as '***no emesis and no rescue therapy*** on days 1–5 postcisplatin', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt's disclosure is generally directed to "treatment of nausea and vomiting from chemotherapy." *Id.*, Abstract. A POSA therefore would have understood Herrstedt's prophylactic triple drug combination is a method for treating both nausea and vomiting (*see* Claim 1) and that the nausea and vomiting is chemotherapy-induced nausea and vomiting (CINV).

313. Accordingly, it is my opinion that claim 15 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

H. Claim 16

> **15.** The method of claim 1, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

314. Claim 16 additionally recites that the nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

315. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

316. Herrstedt discloses wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. As detailed above, Herrstedt discloses its triple drug prophylactic combination is administered for treatment of nausea and vomiting induced by chemotherapy. *See* Claim 15, above. Herrstedt also describes efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***." EX1010 (Herrstedt), Abstract. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of ***cyclophosphamide plus an anthracycline***. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt also includes a table of chemotherapies and classifies cisplatin as highly emetogenic. *Id.*, Table 1. Another of Herrstedt's tables categorizes the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic. *Id.*, Table 4. Thus, the studies described above in Herrstedt evaluating the triple drug combination therapy are used to treat nausea and vomiting induced by moderately or highly emetogenic chemotherapy. EX1010 (Herrstedt), 146.

317. Accordingly, it is my opinion that claim 16 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

I. Claim 17

> **17.** The method of claim 1, comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

318. Claim 17 additionally recites that the method comprises administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

319. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

320. Herrstedt discloses administering moderately or highly emetogenic chemotherapy in conjunction with administering the NK_1 receptor antagonist. Herrstedt provides a summary of two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, above. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Hoffmann) was obvious. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

321. A POSA reviewing Herrstedt would have understood that the chemotherapy in Herrstedt was administered within from about one hour to about two hours of the NK_1 receptor antagonist, consistent with routine practice. *See*,

e.g., EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist aprepitant administered one hour prior to cisplatin); EX1037 (Hesketh), 4113 (same); EX1014 (Bös), 19:15-20 (NK_1 receptor antagonist netupitant administered up to two hours before emetogen). Poli-Bigelli and Hesketh both expressly confirm that the highly emetogenic chemotherapy (cisplatin) was administered one hour after the administration of the NK_1 receptor antagonist (aprepitant). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin, patients received either aprepitant or placebo***. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing aprepitant one hour prior to administration of cisplatin (and in combination with the other drugs disclosed in the regimen) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin, patients received either aprepitant or placebo***. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer moderately or highly emetogenic

chemotherapy within from about one hour to about two hours of the administration of netupitant or pharmaceutically acceptable salt thereof, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

322. Accordingly, it is my opinion that claim 17 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

J. Claim 18

> **18.** The method of claim 1, comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

323. Claim 18 additionally recites that the method comprises treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

324. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Hoffmann, and Hargreaves.

325. Herrstedt discloses treating nausea and vomiting in response to highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 (“cisplatin-based, highly

emetogenic chemotherapy"); *see also* Claim 16, above. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

326. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt treated nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and in response to highly emetogenic chemotherapy during the delayed phase. For example, Herrstedt describes its triple-therapy dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.,* 143. Poli-Bigelli expressly confirms the triple-therapy dosing combination treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096.

327. Hesketh also confirms the triple-therapy dosing combination of Herrstedt treats nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

Therefore, a POSA would have had good reason to prophylactically administer the triple drug combination of Herrstedt, employing netupitant from Hoffmann, and would have had a reasonable expectation of success that such dosing would treat nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and also would treat nausea and vomiting in response to highly emetogenic chemotherapy during the delayed phase.

328. Accordingly, it is my opinion that claim 18 as a whole was also obvious over Herrstedt, Hoffmann, and Hargreaves.

K. Claim 24

24. The method of claim 1, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK_1 activity.

329. Claim 24 depends from claim 1 and further requires that palonosetron and netupitant are "synergistically effective to antagonize NK_1 activity." I see no definition of "synergistically effective to antagonize NK_1 activity" in the '826 patent. Nor do I see disclosure of synergy in the specification. But any alleged synergistic effect is an inherent quality of palonosetron and netupitant being co-administered in therapeutic amounts. Patent applicant asserted as much during prosecution of the '050 application. EX1008 (file history of '050 application), 186 ("At ***all*** concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined."). As I described above, the combination of Herrstedt, Hoffmann, and Hargreaves rendered obvious co-administering netupitant and palonosetron. *See* Section XIV.A, above.

330. In addition to the inherency admission by the patentee before the Patent Office, recent studies also confirm any synergy is inherent to the co-administration that I've explained above was obvious. The literature reasons that "both netupitant and palonosetron can trigger NK_1 receptor internalization." EX1045 (Thomas), 2643; *see also id.*, 2642. Palonosetron—a 5-HT_3 receptor antagonist—affects NK_1 receptors "through a 5-HT_3 receptor-mediated effect" between the 5-HT_3 and NK_1 receptors. *Id.* The literature identifies this internalization as "***a mechanistic explanation of*** the additive and ***synergistic***

effects on the NK_1 receptor antagonism when a combination of netupitant and palonosetron is used in these cells." *Id*. (emphasis added); *see also* EX1041 (Rojas), 365, 368 (unlike other 5-HT_3 receptor antagonists, palonosetron triggered internalization of 5-HT_3 receptors, affecting the "5-HT3 and NK-1 receptor pathways in a dose- and time-dependent fashion"). These post-critical date publications identify the NK_1-receptor-internalization-property of palonosetron as a property intrinsic to that prior art 5-HT_3 receptor antagonist. Any alleged additive or synergistic effect on NK_1 receptor antagonism is thus inherent to the obvious combination of therapeutically-effective amounts of palonosetron and an NK_1 receptor antagonist.

331. Because the additive/synergistic effect is an inherent property that naturally results from administering therapeutically effective amounts of palonosetron and an NK_1 receptor antagonist—a combination that Herrstedt teaches is favorable particularly for palonosetron's additional efficacy for treating delayed emesis—this allegedly unexpected result is merely an inherent property of a prior art or at least an obvious combination.

332. Accordingly, it is my opinion that claim 24 was obvious as a whole over Herrstedt, Hoffmann, and Hargreaves.

L. Motivation to Combine

333. By November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the triple antiemetic combination therapy provided in Herrstedt, using therapeutically effective amounts of the new NK_1 and 5-HT_3 receptor antagonists as claimed.

334. As an initial matter, persons having ordinary skill in the art would have had good reason to prophylactically treat patients receiving highly and moderately emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt triple therapy to provide antiemetic effect. Herrstedt describes the three-drug combination of 5-HT_3 receptor antagonist (ondansetron), NK_1 receptor antagonist (aprepitant), and dexamethasone administered on Day 1 yielded superior response rates (complete response) compared to the two-drug combination lacking an NK_1 receptor antagonist. EX1010 (Herrstedt), 146 ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm (P = 0.003)."); *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 and NK_1 receptor antagonists administered with dexamethasone on Day 1 (prior to chemotherapy) provided antiemetic effect).

335. A person having ordinary skill in the art would have modified the Herrstedt triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron. The POSA would have expected continued efficacy of the antiemetic drug combination of Herrstedt with new drugs targeting the same mechanistic pathways. Palonosetron was known to have an order of magnitude greater half-life than the ondansetron evaluated in Herrstedt's comparative study design. *Id.*, 146 & Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours). Additionally, palonosetron was known to be available in an oral formulation (0.56 mg palonosetron HCl). EX1015 (Aloxi); EX1052 (RxList); EX1053 (DailyMed); EX1054 (DailyMed Archived). The POSA would have been motivated to administer to the patient the oral form of palonosetron HCl as the 5-HT_3 receptor antagonist for ease to both patient and practitioner, as well as for improved patient perception and comfort, as described above.

336. The person having ordinary skill in the art also would have modified the Herrstedt triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the antiemetic drug combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt drug combination to replace NK_1 receptor antagonist aprepitant with Hoffmann's NK_1 receptor antagonist

netupitant because, as Hoffmann explains, netupitant was shown "to potently inhibit NK_1 agonist-induced foot tapping…after oral administration" which was indicative of successful NK_1 receptor antagonism, and also identified netupitant as having "[e]xcellent oral antagonist activity." EX1011 (Hoffmann), 1364-1365. Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by replacing aprepitant with netupitant, and would have had a reasonable expectation of success in doing so.

337. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, as of the critical date, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

338. Accordingly, persons having ordinary skill in the art would have had good reason to employ the new 5-HT_3 receptor antagonist (palonosetron) and Hoffmann's NK_1 receptor antagonist (netupitant) with dexamethasone as claimed

in the Herrstedt triple active combination therapy to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

339. The POSA would have had good reason to apply NK_1 receptor occupancy studies, such as those disclosed in Hargreaves, to evaluate appropriate doses yielding therapeutic effect.

M. Reasonable Expectation of Success

340. Persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt triple active combination therapy with the claimed netupitant and palonosetron therapeutics. Herrstedt teaches that the art had used alternative 5-HT_3 receptor antagonists to treat CINV. EX1010 (Herrstedt), 146. Herrstedt explicitly envisions the substitution of palonosetron, the new 5-HT_3 receptor antagonist, and other therapeutic agents into the antiemetic drug combination. *Id.*, 145 ("Palonosetron, the newest of these agents, has a very potent and specific binding at 5-HT_3 receptor and a half-life around 40 hr as compared to less than 10 hr for the other agents."). Furthermore, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome.

Because both palonosetron and ondansetron were known to achieve the desired therapeutic effect via the same mechanism—by antagonizing the 5-HT_3 receptor—the POSA would have reasonably expected therapeutically effective amounts of palonosetron and ondansetron to achieve at least a comparable effect of anti-emesis. EX1010 (Herrstedt), 145-146 & Table 3. That palonosetron was known to have favorable qualities as compared to ondansetron (as I describe above) means the POSA would have reasonably expected that palonosetron would improve or be similar to the Herrstedt antiemetic drug combination as compared to the standard therapy (using ondansetron, without NK_1 receptor antagonist).

341. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve a similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1011 (Hoffmann), 1362. Thus, a POSA would have expected therapeutically effective amounts of aprepitant and netupitant to achieve comparable anti-emetic and anti-nausea effects or better when administered on

Day 1 (prior to chemotherapy). *See also* EX1016 (Herrington), Abstract, 2084 (NK_1 receptor antagonist administered on Day 1 provided antiemetic effect). That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant.

342. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves. Hargreaves describes therapeutic effect correlates with NK_1 receptor occupancy (EX1012 (Hargreaves), 23 & Fig. 6(B)) and explains its study protocol could be used to evaluate when a dose is sub-therapeutically effective or therapeutically effective, with no additional therapeutic effect observed for oversaturating the NK_1 receptors. *Id.* Thus, a POSA would have had a reasonable expectation of success in determining the therapeutically effective dose of netupitant applying the same protocol.

343. Accordingly, the POSA had good reason to combine Herrstedt, Hoffmann, and Hargreaves to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XV. [’826 PATENT GROUND 5] ’826 PATENT CLAIMS 1-3, 6-10, 15-18, AND 24 WERE OBVIOUS OVER HERRSTEDT, BÖS & HARGREAVES

344. For the reasons discussed in detail below, it is my opinion that each of claims 1-3, 6-10, 15-18, and 24 of the ’826 patent was obvious as a whole. The obviousness of claims 1-3, 6-10, 15-18, and 24 is exemplified by disclosures in the Herrstedt, Bös, and Hargreaves references.

345. I have evaluated below whether the combination of Herrstedt, Bös, and Hargreaves discloses each and every element of each of claims 1-3, 6-10, 15-18, and 24 of the ’826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal “yes.”

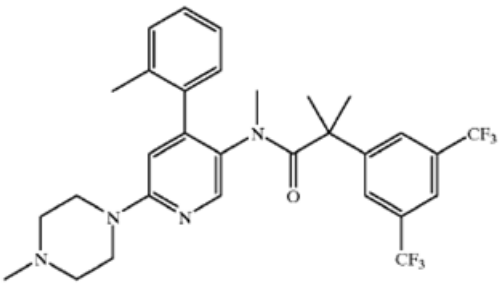
346. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010 (Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt discloses administering to the patient on day one a therapeutically effective amount of a 5-HT_3 receptor antagonist (EX1010 (Herrstedt), 146) and teaches that palonosetron is a new 5-HT_3 receptor antagonist (*Id.*). Herrstedt also discloses administering to the patient on day one a first dose of

dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps in the dosing regimen are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146. Further, Herrstedt describes the above steps are effective for treating both nausea and vomiting to a greater extent during the 5-day period as compared to a drug combination of just the 5-HT_3 receptor antagonist and dexamethasone. *Id.*, 146-147. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

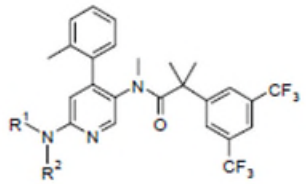
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

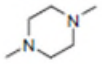
EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*, 17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced

behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

347. For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in Herrstedt.

348. Hargreaves explains NK_1 receptor occupancy of greater than 75% is associated with therapeutic effectiveness. EX1012 (Hargreaves), Abstract, 23, Fig. 6B. Hargreaves also teaches to measure NK_1 receptor occupancy in the striatum. As I explain further below, a POSA would have understood the therapeutically effective dose of netupitant would likely occupy at least 75% of NK_1 receptors in the striatum after prophylactic administration. Section XV.A. The skilled artisan would have reasonably expected that a prophylactically administered therapeutically effective dose of netupitant (e.g., 300 mg) would naturally result in

very high occupancy of NK_1 receptors in the striatum (e.g., greater than 70%) and that due to netupitant's long half-life, it is a natural result that there would still be high occupancy of the striatum NK_1 receptors at 72 hours.

349. The sections below explain in more detail how Herrstedt, Bös, and Hargreaves disclose each and every element of claims 1-3, 6-10, 15-18, and 24. I first analyze independent claim 1 of the challenged '826 patent. Thereafter, I analyze dependent claims 2-3, 6-10, 15-18, and 24.

A. Claim 1

1[pre]. A method of treating both nausea and vomiting for five consecutive days in a patient in need thereof, comprising:

350. I have reproduced above the preamble of claim 1 of the '826 patent. Herrstedt teaches a "method of treating both nausea and vomiting for five consecutive days in a patient in need thereof" as disclosed in the preamble of claim 1. For example, Herrstedt teaches methods for prophylactically treating "[c]hemotherapy-induced ***nausea and vomiting***" in a patient. EX1010 (Herrstedt), 143. Herrstedt describes its primary therapeutic endpoint was no emesis for five consecutive days following administration of the chemotherapeutic, cisplatin (i.e., five days "postcisplatin"). *Id.*, 146 ("Complete response, defined as 'no emesis and no rescue therapy on days 1–5 postcisplatin', was the primary end-point in all studies."). Accordingly, the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in the preamble of claim 1.

1(a)[1]. a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof,

351. I have reproduced above the administering step (a)[1] element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the administering step of claim 1(a)[1].

352. Herrstedt expressly discloses multiple studies for treatment of highly-emetogenic chemotherapy in patients with a triple-drug combination administered to patients on day one including an NK_1 receptor antagonist (aprepitant). EX1010 (Herrstedt), 146 ("Two of the HEC studies used an identical design…ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes benefits to patients receiving the triple-drug antiemetic combination (including NK_1-receptor antagonist) administered on day one. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm."); *see also* EX1016 (Herrington), Abstract, 2084 (NK_1 receptor antagonist administered on Day 1, prior to chemotherapy, provided antiemetic effect).

353. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the

first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for

treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

354. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective oral dose.

355. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the

importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt

combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

356. Accordingly, Herrstedt discloses administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of netupitant for treatment of nausea and vomiting, such as in the method disclosed in Herrstedt.

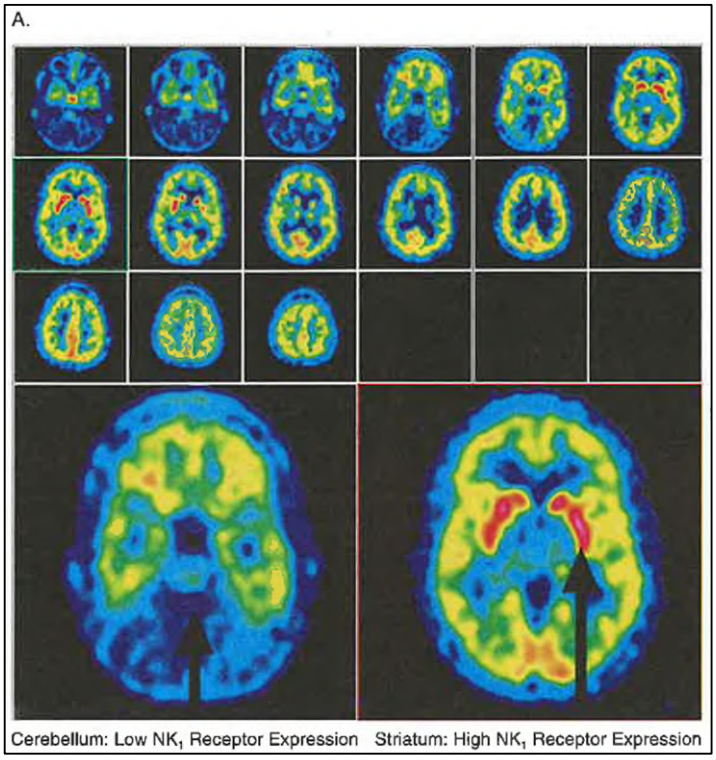
> **1(a)[2].** In a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK) receptors in the striatum seventy-two hours after said administration;

357. I have reproduced above the therapeutically effective amount (a)[2] element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the therapeutically effective amount of claim 1(a)[2].

358. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of compounds that are administered orally. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be

appropriate"). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

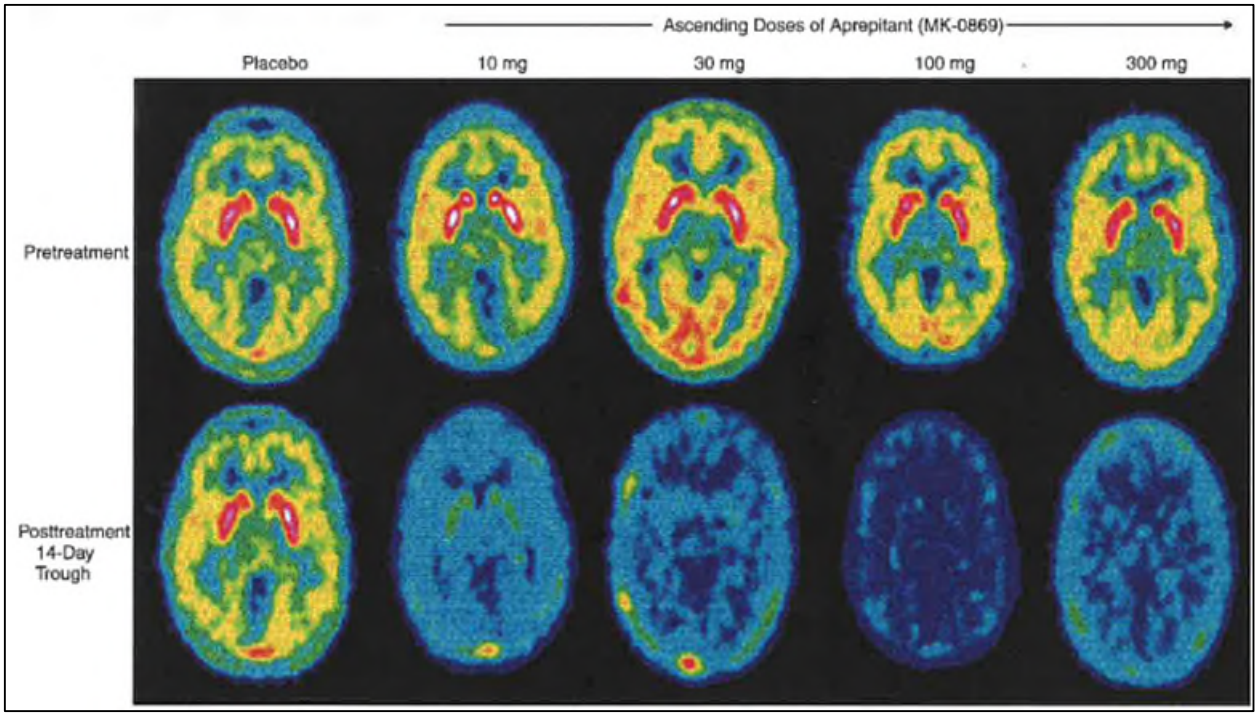
359. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).

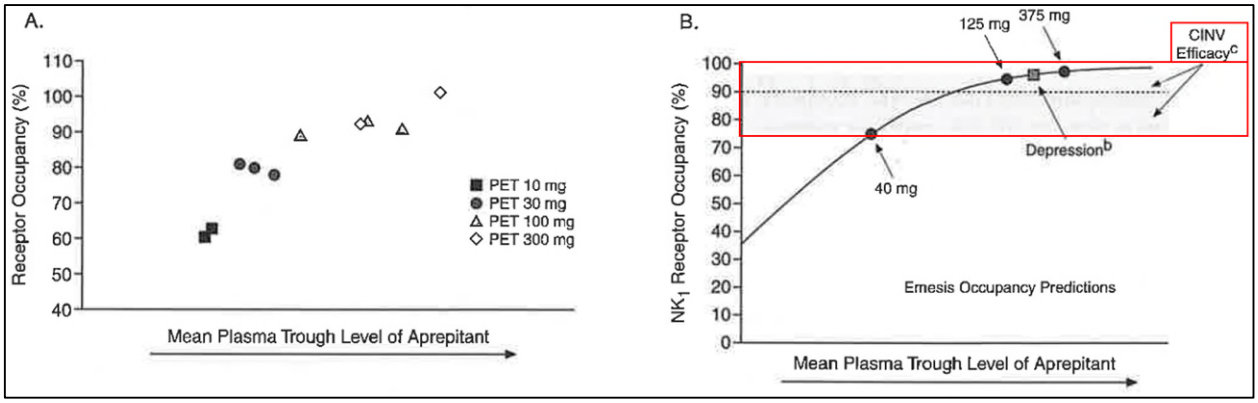


360. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS

(Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



EX1012 (Hargreaves) Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the therapeutically effective amount of claim 1(a)[2]. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

361. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally

accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Sections V.C-V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See*, *e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Sections V.C-V.D, above. The '826 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration." EX1001 ('826 patent), 4:37-51. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

362. Accordingly, the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(a)[2].

> **1(b).** b) administering to said patient on day one a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof; and;

363. I have reproduced above the administering step (b) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the administering step of claim 1(b).

364. Herrstedt teaches or suggests administering a therapeutically effective amount of palonosetron to said patient on day one. For example, Herrstedt identifies palonosetron as a favorable 5-HT_3 receptor antagonist for treating emesis. EX1010 (Herrstedt), 146. Herrstedt specifically teaches palonosetron differed from other 5-HT_3 receptor antagonists because it showed beneficial properties "in the treatment of delayed emesis from MEC" and also had an order of magnitude increase in half-life as compared to the 5-HT_3 receptor antagonist ondansetron. *Id.*, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours); *see also id.*, 146 ("in the MEC studies some of the evaluable parameters ***significantly favoured palonosetron***."). Herrstedt further describes palonosetron as a suitable substitution for ondansetron for treating emesis, stating: "Palonosetron has been compared to ondansetron and dolasetron in three randomized, double-blind trials" and each "demonstrated that palonosetron was not

inferior to dolasetron and ondansetron." *Id.*, 146. Thus, a POSA would have had good reason to employ a therapeutically effective amount of the "significantly favoured" palonosetron as the 5-HT_3 receptor antagonist to said patient. Furthermore, the POSA would have had a reasonable expectation of success in making such a substitution because both palonosetron and ondansetron worked through an identical mechanism (i.e., 5-HT_3 receptor antagonism) to achieve the same therapeutic result (i.e., anti-emesis).

365. Herrstedt also expressly disclosed the therapeutically effective amount of 5-HT_3 receptor antagonist should be administered to said patient on day one. For example, Herrstedt explains that a therapeutically effective amount of the 5-HT_3 receptor antagonist is administered to the patient on day one in both the standard study (5-HT_3 receptor antagonist and dexamethasone) and the study evaluating triple therapy adding NK_1 receptor antagonist:

> Two of the HEC studies used an identical design comparing ***ondansetron***, dexamethasone and placebo ***day 1*** followed by dexamethasone plus placebo days 2-4 with ***ondansetron***, dexamethasone and aprepitant ***day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3.

EX1010 (Herrstedt), 146. Herrstedt explains that latter studies copied this dosing of 5-HT_3 receptor antagonist on day 1 prior to chemotherapy. *Id.* ("The most

recently published HEC study used the same design, except that ondansetron was [also] included in the control arm for delayed protection days 2-4.").

366. Accordingly, the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(b).

> **1(c).** c) administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant,

367. I have reproduced above the administering step (c) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the administering step of claim 1(c).

368. As I explained above, before looking to evaluate whether the prior art discloses this limitation, I look to the specification of the '826 patent exclusively to understand what the claim means when it says a first dose of dexamethasone is "ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with said netupitant." For example, the specification admits that a 20 mg dose of dexamethasone was known in the field as the minimum day-one therapeutically effective dose for treating CINV:

> The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be ***20 mg***. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two,

> three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the ***minimum effective dose of dexamethasone*** is ***20 mg***. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1001 ('826 patent), 7:62-8:4 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). As defined in the patent specification, the claim term "dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone" encompasses any day one dose of less than 20 mg. The prior art routinely described this same 20 mg dose as the standard day one dose for treating emetogenic chemotherapy. *See, e.g.*, EX1010 (Herrstedt), 145 ("single intravenous dose of 20 mg" for highly emetogenic chemotherapy); EX1025 (Chawla), 2292 (standard therapy combination included oral dexamethasone 20 mg on Day 1 prior to chemotherapy); EX1013 (MASCC), Table 3 (20 mg dexamethasone for patients not receiving aprepitant).

369. Understanding the claim term as illustrated in the patent specification, Herrstedt discloses administering to said patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with the NK_1 receptor antagonist. For example,

Herrstedt teaches administering a single, sub-20 mg day one dose of dexamethasone for the treatment of moderately emetogenic chemotherapy, a treatment that leads to CINV. EX1010 (Herrstedt), 145-147. In contrast to the standard 20 mg day one dose, Herrstedt teaches that the day one dexamethasone should be administered in a reduced amount—about 25% to 50% less than the 20 mg (minimally effective) standard dose discussed above. *Id.* Such reduced amount was, by itself, ineffective against CINV, but when administered with the combination of therapeutics (including 5-HT_3 and NK_1 receptor antagonists), the reduced amount of dexamethasone was effective against CINV.

370. Herrstedt explains that due to metabolic interactions of corticosteroids (e.g., dexamethasone or methylprednisolone) and the NK_1 receptor antagonist (aprepitant), the corticosteroid should be administered in a lower-than-typically-therapeutic dose when treatment includes the NK_1 receptor antagonist. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

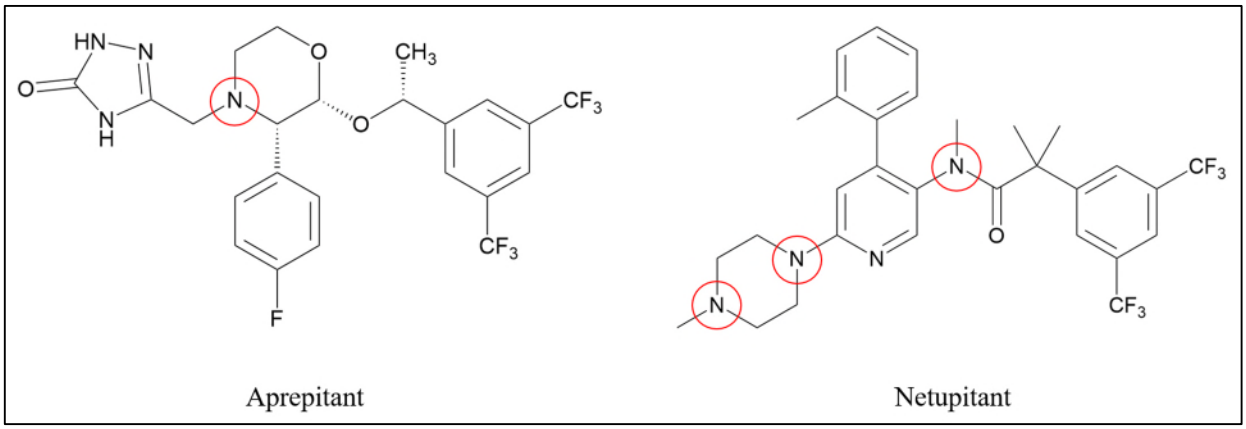
> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Therefore Herrstedt suggests the dose of dexamethasone—when administered with NK_1 receptor antagonist—should be a reduced dose which, by itself would be ineffective against CINV, but when administered in combination with NK_1 receptor antagonist is effective against CINV because it provides the same total exposure of dexamethasone AUC. Thus, Herrstedt describes administering to the patient on day one a first dose of dexamethasone which is ineffective against chemotherapy induced nausea and vomiting (CINV) when administered alone, but effective against CINV when administered in combination with the NK_1 receptor antagonist.

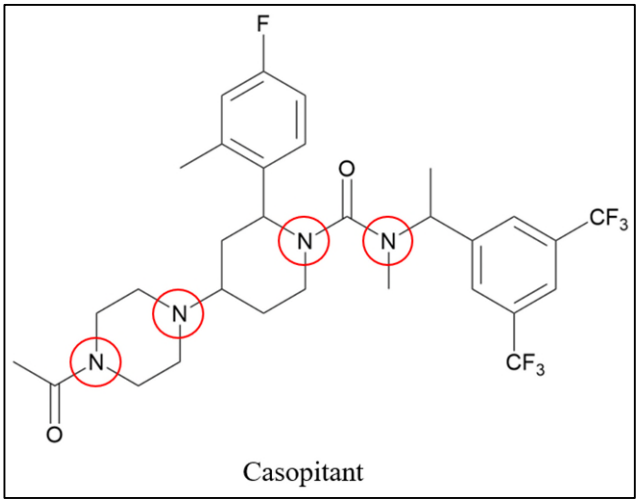
371. Based on the experience with aprepitant, a POSA would have had good reason to determine the dexamethasone AUC when administered with netupitant compared to administration of dexamethasone alone. Evaluating such drug-drug interactions was well-known and routine in the field. EX1049 (Zhou), 318 ("Drug-drug interactions remain an important issue in clinical practice and drug development"). Evaluating such drug-drug interactions (e.g., NK_1-receptor-antagonist-induced dexamethasone potentiation) was a fundamental prerequisite

when administering a combination therapy, such as the combination antiemetic therapy at issue. EX1010 (Herrstedt), 147 ("Risk of drug-drug interactions with the use of anti-emetics" due to "concomitant treatment with supportive care drugs" should be evaluated). Understanding the interaction of therapeutic agents with their metabolism provided necessary insight for evaluating drug-drug interactions. EX1044 (Schoenwald), 86 ("By understanding which metabolic steps may be susceptible to induction or inhibition by other drugs, specific *in vitro* or clinical drug interaction studies may be conducted to determine the potential risks of drug-drug interactions."). Among other interactions, a POSA would have had good reason to measure the impact of netupitant administration on the cytochrome P450 (CYP) 3A4 ("CYP3A4") enzyme-mediated metabolism of dexamethasone. This particular cytochrome P450 was known to "metaboliz[e] more than 50% of [] clinically used drugs." EX1049 (Zhou), 310. In addition to metabolizing "more than 50% [of] therapeutic drugs" CYP3A4 was known to have "very broad" substrate specificity "with an extremely large number of structurally divergent chemicals being metabolized." *Id.*, 311. In other words, it was well-known CYP3A4 had high "ligand promiscuity" for metabolism and a high likelihood of being involved in the metabolism of a given therapeutic agent. *Id.* Additionally, CYP3A4 was known to be inhibited by a variety of substrates sharing common structural features with aprepitant and netupitant. For example, drugs known to

inactivate CYP3A4 "often possess a number of structural similarities such as a tertiary amine function[.]" EX1049 (Zhou), 314. Both aprepitant and netupitant had such tertiary amine function, as shown in the below figure (red circles annotating tertiary amines).



It was known that aprepitant was a substrate and moderate inhibitor of CYP3A4, leading to increased AUC exposure of dexamethasone. EX1010 (Herrstedt), 147; Sections IX.A, IX.E, above (50% increase of dexamethasone AUC). Likewise, it was known that the NK_1 receptor antagonist casopitant—structurally similar to netupitant—was also a substrate and weak-to-moderate inhibitor of CYP3A4, requiring "a reduction in dexamethasone dose of 40-50%, when repeat-dose oral dexamethasone is to be co-administered with oral casopitant." EX1042 (Ruhlmann), 377-378; *see also* the below figure where I provide the structure with annotations of tertiary amines.



Casopitant

Thus, a POSA would have expected netupitant to similarly act as substrate and inhibitor of CYP3A4. Accordingly, it would have been obvious and routine to a POSA in view of Herrstedt, Bös, and Hargreaves to measure the impact of netupitant co-administration on dexamethasone AUC and to lower the dexamethasone dose accordingly. Because the patent defines the sub-therapeutic dose of dexamethasone to encompass any day one dose below the standard 20 mg dose, any actual reduction from the standard day one dose satisfies the claims.

372. Having good reason to co-administer netupitant with dexamethasone (as discussed above), the reduced metabolism of dexamethasone when co-administered with netupitant is a property that necessarily and naturally flows from the combination. Accordingly, a POSA performing routine metabolism studies on the combination therapy would reasonably expect to measure the increased dexamethasone AUC and to reduce the dexamethasone dose below the 20 mg

(minimally effective) standard dose, which dose reduction the patent itself admits satisfies the claim.

373. Accordingly, it is my opinion that the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(c).

> **1(d).** wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

374. I have reproduced above the decreased dexamethasone dose (d) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the decreased dexamethasone dose of claim 1(d).

375. As I explained above for element 1(c), Herrstedt explains the day one dose of dexamethasone should be administered in a reduced amount—including by about 50 to 70%—compared to the 20 mg dose. As I explained above, it was known NK_1 receptor antagonists doubled the AUC concentration of dexamethasone, and Herrstedt teaches reducing the dexamethasone dose in a corresponding amount. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone,

when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Herrstedt thus teaches reducing the day one dose of oral dexamethasone, when administered with an NK_1 receptor antagonist, by about 50% of the minimum effective dose when administered alone to achieve the same effective AUC concentration. Furthermore, Herrstedt discloses that administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study," each of which discloses the first dose of dexamethasone comprises 12 mg (60% of the 20 mg minimum effective dose), confirming that Herrstedt teaches reducing the day one dose. EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)); EX1039 (Poli-Bigelli), Abstract ("oral dexamethasone 12 mg on Day 1"); EX1037 (Hesketh), 4113 ("oral dexamethasone 12 mg on day 1"). Accordingly, Herrstedt discloses element 1(d). *See also* Sections IX.A, IX.E, above (prior art taught to reduce dexamethasone when administered with NK_1 receptor antagonists).

376. Accordingly, it is my opinion that the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(d).

> **1(e).** steps a, b and (c) are effective to treat both nausea and vomiting during the period defined by days one through five; and

377. I have reproduced above the efficacy (e) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the efficacy of claim 1(e).

378. Herrstedt teaches or suggests each of steps (a), (b), and (c) of claim 1, as I detailed above, with Bös suggesting netupitant. Herrstedt teaches that the steps are effective to treat both nausea and vomiting over a treatment period defined by days one through five:

> Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. ***Complete response, defined as "no emesis and no rescue therapy on days 1-5 postcisplatin," was the primary end-point in all studies***. Two of the HEC studies used…ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, a complete response of 72.7% in the aprepitant arm versus 53.3% in the control arm was seen[.]

EX1010 (Herrstedt), 146. Herrstedt describes its triple therapy combination (5-HT_3 receptor antagonist, dexamethasone, and NK_1 receptor antagonist) is recommended "for ***prevention of acute and delayed nausea and vomiting***." *Id.*, 148 & Table 4 (MASCC guidelines). The acute time period (0-24 hours) and delayed time period (24-120 hours) encompasses days one through five. *Id.*, 143.

379. Accordingly, the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(e).

> **1(f).** steps (a), (b) and (c) are effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five than steps (b) and (c) alone.

380. I have reproduced above the efficacy (f) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests the efficacy of claim 1(f).

381. As described above, the combination of Herrstedt, Bös, and Hargreaves teach the triple therapy of steps (a) (administering NK_1 receptor antagonist netupitant), (b) (administering 5-HT_3 receptor antagonist palonosetron), and (c) (administering dexamethasone) is more effective than the standard therapy (administering 5-HT_3 receptor antagonist with dexamethasone). EX1010 (Herrstedt), 146 (adding NK_1 receptor antagonist aprepitant improved response rates in all studies). Claim element 1(f) further requires that the triple therapy is "effective to treat both nausea and vomiting to a greater extent during the period defined by days one through five" than the standard therapy (5-HT_3 receptor antagonist with dexamethasone). In other words, this claim element is directed at showing that administering the NK_1 receptor antagonist netupitant improves treatment of both nausea and vomiting during the period defined by days one through five (i.e., the combined acute and delayed phases).

382. Herrstedt explicitly teaches improved effectiveness to treat both nausea and vomiting with the triple therapy (NK_1 receptor antagonist, 5-HT3 receptor antagonist, and corticosteroid) as compared to the corresponding combination without the NK_1 receptor antagonist. For example:

> Complete response, defined as "no emesis and no rescue therapy on days 1-5 postcisplatin," was the primary end-point in all studies. Two of the HEC studies used an identical design comparing ***ondansetron [5-HT3 receptor antagonist], dexamethasone [corticosteroid], and placebo*** day 1 followed by dexamethasone plus placebo days 2-4 with ***ondansetron, dexamethasone and aprepitant [NK_1 receptor antagonist]*** day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, ***a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen***, and in the Poli-Bigelli study complete response rates were 62.7% versus 43.3%. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2-4. Again a ***statistical[] benefit favouring aprepitant was seen***, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.

EX1010 (Herrstedt), 146 (parentheticals omitted). The POSA would have understood that the addition of NK_1 receptor antagonist increased overall efficacy of the therapy. Herrstedt explains its triple therapy was recommended as the new and improved standard for treating highly emetogenic chemotherapy because it facilitated "prevention of ***acute and delayed nausea and vomiting***." EX1010

(Herrstedt), 148 & Table 4 (MASCC recommendations). Because each of the drugs in the combination targets a different mechanism providing relief for a patient suffering from nausea and vomiting, the POSA would have had good reason to combine the medications with a reasonable expectation of success in further improving both nausea and vomiting following CINV during both the acute and delayed period (i.e., during the period defined by days one through five).

383. Accordingly, the combination of Herrstedt, Bös, and Hargreaves discloses the subject matter recited in claim element 1(f).

384. The combination of Herrstedt, Bös, and Hargreaves thus teaches all of the elements of claim 1 and rendered the claim obvious as a whole.

B. Claim 2

> **2.** The method of claim 1, further comprising: d) administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

385. Claim 2 additionally recites that the method is further comprising: (d) administering to said patient, on days two, three and four, a second dose (i.e., having a different strength from day one) of dexamethasone which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with steps (a) and (b), wherein said

second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting.

386. As I have previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

387. Herrstedt describes its method further comprises administering to said patient, on days two, three, and four, a second dose (i.e., having a different strength from day one) of dexamethasone. Herrstedt identifies several studies having such dosing:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, dexamethasone and aprepitant day 1 followed by ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

EX1010 (Herrstedt), 146; *see also* Section XV.A, above (routine protocol to dose dexamethasone on subsequent days).

388. Herrstedt suggests the days 2-4 doses of dexamethasone are ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with: (a) administering an NK_1 receptor antagonist and (b) administering a 5-HT_3 receptor antagonists. Herrstedt teaches that a lower dose of corticosteroids, such as

dexamethasone, should be administered when concomitantly administered with an NK_1 receptor antagonist due to resulting increase of AUC exposure. EX1010 (Herrstedt), 147-148; *see also* Sections XV.A, IX.E, above. Thus, when the lower dose of dexamethasone is administered alone against HEC-induced vomiting (i.e., in absence of NK_1 receptor antagonist) it is ineffective against vomiting, but when administered in combination with the NK_1 receptor antagonist and 5-HT_3 receptor antagonist, the lower dose is effective in increasing the efficacy of the combination treatment. *See also* Section XV.A, above (known CYP3A4 metabolism interaction and corresponding decrease of dose of dexamethasone).

389. Herrstedt also suggests said second dose comprises from 40 to 60% of a minimum effective dose when administered alone against vomiting. EX1010 (Herrstedt), 146-147. Herrstedt teaches when corticosteroid (e.g., methylprednisolone) is orally administered with NK_1 receptor antagonist, the dose should be reduced "by 50% to obtain the same exposure." EX1010 (Herrstedt), 147. This is an amount which is ineffective against vomiting when administered alone against vomiting, but effective against vomiting when administered in combination with NK_1 and 5-HT_3 receptor antagonists. Herrstedt explains dexamethasone and methylprednisolone are both sensitive to CYP3A4 in the same manner, thus a 50% reduction should be applied to both. EX1010 (Herrstedt), 147. I explained above that NK_1 receptor antagonists doubled the AUC concentration of

dexamethasone, thus it was obvious to correspondingly halve the dexamethasone dose. *See* Sections XV.A, IX.E, above; EX1010 (Herrstedt), 147. As I explained above, a POSA would have expected similar increase in dexamethasone AUC exposure following administration of netupitant. *See* Section XV.A, above. Furthermore, Herrstedt discloses that administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study," each of which discloses the subsequent doses of dexamethasone comprise 8 mg (50% of the 16 mg minimum effective dose (Section XV.A, above; EX1001 ('826 patent), 7:62-8:4 ("The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, ***has been demonstrated to be***…***sixteen mg.*** administered orally or by injection ***on days two, three and four***") (citing EX1019 (Jordan)))), confirming that Herrstedt teaches reducing the day one dose. EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)); EX1039 (Poli-Bigelli), Abstract ("oral dexamethasone ***8 mg once daily on Days 2-3***; and oral dexamethasone ***8 mg on Day 4***"); EX1037 (Hesketh), 4113 (similar). Herrstedt also teaches an effective amount of NK_1 receptor antagonist is present in the patient in subsequent days. For example, when aprepitant is used as the NK_1 receptor antagonist, the literature taught dosing on days 2-3 (EX1010 (Herrstedt), 146), and it was known netupitant had increased receptor affinity and increased half-life (EX1014 (Bös), 19:3-10 (24-30 hours)).

390. Accordingly, the POSA would have good reason to administer doses of dexamethasone on days two, three, and four in a reduced amount to account for increased AUC exposure based on the continued presence of the NK_1 receptor antagonist. Because NK_1 receptor antagonist doubled dexamethasone AUC, a POSA would have reduced the dexamethasone dose by about 50% to obtain the same total AUC concentration. This reduced amount (50% of the minimally effective dose) of dexamethasone would have been ineffective for antiemetic effect when administered as a monotherapy, but would be expected to be effective when combined with NK_1 receptor antagonists due to the increased AUC concentration. *See also* Section XV.A, above (known to administer dexamethasone in a reduced dose on days subsequent to chemotherapy treatment when therapy included an NK_1 receptor antagonist).

391. Accordingly, it is my opinion that claim 2 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

C. Claim 3

> **3.** The method of claim 1 or 2, wherein said netupitant occupies at least 80% of NK receptors in the striatum seventy-two hours after said administration.

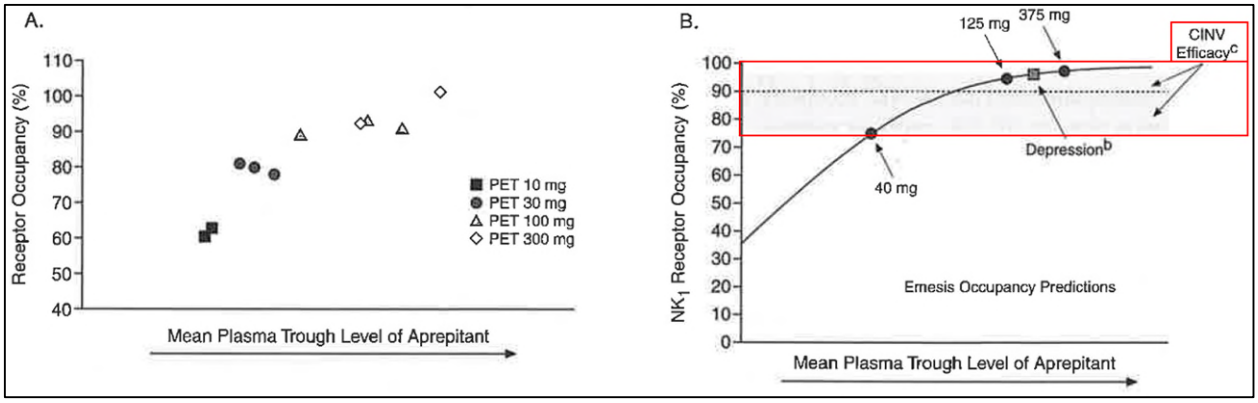
392. Claim 3 additionally recites that the netupitant occupies at least 80% of NK receptors in the striatum seventy-two hours after said administration.

393. I have previously addressed above that each of claims 1 and 2 were obvious over Herrstedt, Bös, and Hargreaves.

394. Hargreaves discloses that there is a direct relationship between occupancy of NK_1 receptors in the striatum and antiemetic effects for patients suffering from chemotherapy-induced nausea and vomiting, and that clinically effective doses of NK_1 receptor antagonists occupy at least 75-80% of NK receptors in the striatum of patients. Hargreaves discloses:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas ***the occupancy of ≥ 90% of NK_1 receptors*** requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of ***emesis blocked ≥ 90% of NK_1 receptors*** in the CNS (Figure 6B), whereas ***the*** initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B).

EX1012 (Hargreaves), 23. Thus, Hargreaves teaches the benefits of the NK_1 receptor antagonist occupying high levels of NK receptors in the striatum (e.g., greater than 90%). Reproduced below is an annotated version of Hargreaves Fig. 6.



Notably, Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy is present in a grayed-out region beginning at approximately 75% of NK_1 receptor occupancy. Thus, Hargreaves explicitly describes that a therapeutically effective amount of an NK_1 receptor antagonist is one which occupies high levels of NK_1 receptors (e.g., greater than 75% and preferably greater than 90%) in the striatum.

395. As described above (Section XV.A), it would have been obvious in view of Hargreaves that a therapeutically effective dose of prophylactically administered netupitant occupies at least 70% of NK_1 receptors in the striatum after administration. As I describe herein, a skilled artisan would have found it obvious to administer 300 mg of netupitant as the therapeutically effective dose (Section XV.E), and because of netupitant's long half-life, it is a natural result that the prophylactic administration of said therapeutically effective dose maintains at least 70% NK_1 receptor occupancy at 72 hours. The "at least 80%" occupancy limitation is substantially similar to the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount

of NK_1 receptor antagonist for the treatment of emesis. EX1012 (Hargreaves), 23 & Fig. 6. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the ’515 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the “at least 80%” occupancy limitation. For example, the examiner stated that netupitant occupying at least 80% of a patient’s striatum NK_1 receptors was an inherent feature of a therapeutically effective dose of netupitant. The examiner also stated that netupitant occupying at least 70% of a patient’s striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant during prosecution of the application that issued as the ’297 patent. EX1008, 120; Section V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner’s position. EX1008, 155; Section V.D, above. The ’826 patent specification reports this is a characteristic of netupitant itself: “netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration.”

EX1001 (’826 patent), 4:37-51. The patentee’s admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

396. Based on Hargreaves’ prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 90% (at least 80%) of NK_1 receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

397. Accordingly, it is my opinion that claim 3 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

D. Claim 6

> **6.** The method of claim 1, wherein said therapeutically effective amount of netupitant comprises from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof.

398. Claim 6 additionally recites that the therapeutically effective amount of netupitant comprises from about 200 to about 400 mg of netupitant or a pharmaceutically acceptable salt thereof.

399. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

400. Bös teaches a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—are in a range that includes from about 200 mg to about 400 mg. Bös discloses a family of NK_1 receptor antagonists including

netupitant are useful for treating chemotherapy-induced emesis. EX1014 (Bös), 2:1-65, 14:9-20. Bös discloses a dose range for its NK_1 receptor antagonists (including netupitant) that encompasses the claimed range from about 200 to about 400 mg. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

401. Bös explicitly recognizes the application of its NK_1 receptor antagonists "for treatment induced vomiting" including "the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist." *Id.*, 1:60-64. Bös describes netupitant and its synthesis (*id.*, 14:9-15:20 (Formula Ib is netupitant)) and explains that netupitant "is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)" (*id.*, 14:32-38). *See also id.*, 18:42-19:38 (favorable in vitro and in vivo studies as well as oral bioavailability and half-life results).

402. It is my opinion that a POSA would have recognized Bös' range spanning two orders of magnitude (about 10 to 1,000 mg) as a favorable starting

point for identifying optimal therapeutic dose amounts. It is my opinion that the POSA would have had good reason to optimize Bös' range when determining the therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22; Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

403. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '826 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '826 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1001 ('826 patent), 7:55-61. Therefore, the '826 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based

on common factors. The POSA therefore would have found it routine to arrive at the 200-400 mg therapeutic dose range of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a range including from about 200 to about 400 mg when determining the therapeutically effective amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

404. Accordingly, it is my opinion that claim 6 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

E. Claim 7

> **7.** The method of claim 1, wherein said therapeutically effective amount of netupitant comprises about 300 mg of netupitant as a free base.

405. Claim 7 additionally recites that the therapeutically effective amount of netupitant comprises about 300 mg of netupitant as a free base.

406. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

407. Bös teaches a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded

when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

408. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, and Hargreaves to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile. A POSA would have had a reasonable

expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating CINV.

409. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the ’826 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the ’826 patent specification, which explains:

> As used herein, “therapeutically effective amount” refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1001 (’826 patent), 7:55-61. Therefore, the ’826 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

410. The ’826 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’826 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1001 (’826 patent), 16:1-36) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1001 (’826 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 16:36-65), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’826 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

411. Accordingly, it is my opinion that claim 7 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

F. Claim 8

> **8.** The method of claim 1, wherein said therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

412. Claim 8 additionally recites that the therapeutically minimum effective dose of dexamethasone when administered alone comprises from about 16 mg to about 20 mg of dexamethasone.

413. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. As described above, it was well known in the field to administer a day-one dose of 20 mg of dexamethasone. *See, e.g.*, EX1010 (Herrstedt), 145 ("In patients receiving cisplatin-based, highly emetogenic chemotherapy (HEC), a single intravenous dose [of dexamethasone] of 20 mg is superior to lower doses…."); *see also* Section XV.A, above. Herrstedt thus disclosed this element. Accordingly, it is my opinion that claim 8 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

G. Claim 9

> **9.** The method of claim 1, wherein only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.

414. Claim 9 additionally recites that only one dose of said palonosetron or a pharmaceutically acceptable salt thereof is administered during said five days.

415. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

416. Herrstedt discloses only one dose of the 5-HT_3 receptor antagonist (e.g., palonosetron, ondansetron) is administered during the five day period. Herrstedt explains:

> Complete response, defined as 'no emesis and no rescue therapy on ***days 1–5 postcisplatin***', was the primary end-point in all studies. Two of the HEC studies used an identical design comparing ***ondansetron***, dexamethasone and placebo ***day 1*** followed by dexamethasone plus placebo days 2–4 with ***ondansetron***, dexamethasone and aprepitant ***day 1*** followed by dexamethasone days 2–4 plus aprepitant days 2–3.

EX1010 (Herrstedt), 146. In other words, the 5-HT_3 receptor antagonist ondansetron was administered only on day one (i.e., there was only one dose of the 5-HT_3 receptor antagonist during the five days). Herrstedt summarizes that the field had embraced administering the 5-HT_3 receptor antagonist in a single dose across the five day period, and suggests that palonosetron should be used as the 5-HT_3 receptor antagonist at least in part because it already also treated delayed emesis:

> Ondansetron and granisetron were initially developed as 8 mg t.i.d. and 3 mg plus up to two additional doses within the first 24 hr after chemotherapy, respectively. ***Today, all these agents are primarily used as a single oral or intravenous dose*** (ondansetron can be given twice daily in patients receiving MEC). Originally ondansetron and granisetron were prescribed for up to 5 days after chemotherapy, but it is now recognized that the 5-HT3-receptor antagonists are primarily

effective in the prophylaxis of acute emesis with limited or no efficacy in delayed emesis. ***Palonosetron might be an exception and it has been approved by the Food and Drug Administration*** (but not by the European Medicines Agency) ***in the treatment of delayed emesis*** from MEC.

Id., 145-146.

417. Furthermore, the POSA would have understood that the increased half-life of palonosetron indicated that the single dose of palonosetron on day 1 of therapy (prior to chemotherapy) would be sufficient to confer the delayed emesis benefit provided by palonosetron. Herrstedt describes that palonosetron has an ***order of magnitude*** greater half-life as compared to ondansetron. *Id.*, Table 3 (below).

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

Therefore, the POSA would have had good reason to prophylactically administer only one dose of palonosetron or a pharmaceutically acceptable salt thereof during the five day treatment period.

418. Accordingly, it is my opinion that claim 9 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

H. Claim 10

10. The method of claim 1, wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

419. Claim 10 additionally recites that the therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

420. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

421. Herrstedt discloses that the clinical dose of palonosetron is within the range of about 0.25 to about 0.75 mg based on the weight of the free base. Herrstedt discloses, in Table 3, that it was known in the art to administer palonosetron in a 0.25 mg intravenous dose.

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

EX1010 (Herrstedt), Table 3. Thus, Herrstedt explicitly discloses the therapeutically effective amount of palonosetron is within the range of from about 0.25 to about 0.75 mg based on the weight of the free base. *See also* Section IX.D, above (0.25 mg to 0.75 mg known to be effective for preventing CINV).

422. Accordingly, it is my opinion that claim 10 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

I. Claim 15

> **15.** The method of claim 1, wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

423. Claim 15 depends from claim 1 and additionally recites that the nausea and vomiting is chemotherapy induced nausea and vomiting, radiation therapy induced nausea and vomiting, ***or*** post-operative nausea and vomiting.

424. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

425. Herrstedt describes its combination therapy is used as a prophylactic to treat nausea and vomiting that is chemotherapy induced nausea and vomiting (CINV). Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as '***no emesis and no rescue therapy*** on days 1–5 postcisplatin', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt's disclosure is generally directed to "treatment of nausea and vomiting from chemotherapy." *Id.*, Abstract. A POSA therefore would have understood Herrstedt's administration of prophylactic triple drug

combination is a method for treating both nausea and vomiting (*see* Claim 1) and that the nausea and vomiting is chemotherapy-induced nausea and vomiting (CINV).

426. Accordingly, it is my opinion that claim 15 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

J. Claim 16

> **15.** The method of claim 1, wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

427. Claim 16 additionally recites that the nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

428. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

429. Herrstedt discloses wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. As detailed above, Herrstedt discloses its triple drug prophylactic combination is administered for treatment of nausea and vomiting induced by chemotherapy. *See* Claim 15, above. Herrstedt also describes efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***." EX1010 (Herrstedt), Abstract. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a

> combination of ***cyclophosphamide plus an anthracycline***. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt also includes a table of chemotherapies and classifies cisplatin as highly emetogenic. *Id.*, Table 1. Another of Herrstedt's tables categorizes the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic. *Id.*, Table 4. Thus, the studies described above in Herrstedt evaluating the triple drug therapy are used to treat nausea and vomiting induced by moderately or highly emetogenic chemotherapy. EX1010 (Herrstedt), 146.

430. Accordingly, it is my opinion that claim 16 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

K. Claim 17

> **17.** The method of claim 1, comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

431. Claim 17 additionally recites that the method comprises administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

432. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

433. Herrstedt discloses administering moderately or highly emetogenic chemotherapy in conjunction with administering the NK_1 receptor antagonist. Herrstedt provides a summary of two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, above. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) was obvious. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

434. A POSA reviewing Herrstedt would have understood that the chemotherapy in Herrstedt was administered within from about one hour to about two hours of the NK_1 receptor antagonist, consistent with routine practice. *See, e.g.*, EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist aprepitant administered one hour prior to cisplatin); EX1037 (Hesketh), 4113 (same); EX1014 (Bös), 19:15-20 (NK_1 receptor antagonist netupitant administered up to two hours before emetogen). Poli-Bigelli and Hesketh both expressly confirm that the highly emetogenic chemotherapy (cisplatin) was administered one hour after the administration of the NK_1 receptor antagonist (aprepitant). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin, patients received either aprepitant or placebo***. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing aprepitant one hour prior to administration of cisplatin (and in combination with the other drugs disclosed in the regimen) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin, patients received either aprepitant or placebo***. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer moderately or highly emetogenic chemotherapy within from about one hour to about two hours of the administration of netupitant or pharmaceutically acceptable salt thereof, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

435. Accordingly, it is my opinion that claim 17 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

L. Claim 18

> **18.** The method of claim 1, comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

436. Claim 18 additionally recites that the method comprises treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

437. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

438. Herrstedt discloses treating nausea and vomiting in response to highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"); *see also* Claim 16, above. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

439. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt treated nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and in response to highly

emetogenic chemotherapy during the delayed phase. For example, Herrstedt describes its triple-therapy dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the triple-therapy dosing combination treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant

nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096.

440. Hesketh also confirms the triple-therapy dosing combination of Herrstedt treats nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

Therefore, a POSA would have had good reason to prophylactically administer the triple drug combination of Herrstedt, employing netupitant from Bös, and would

have had a reasonable expectation of success that such dosing would treat nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and also would treat nausea and vomiting in response to highly emetogenic chemotherapy during the delayed phase.

441. Accordingly, it is my opinion that claim 18 as a whole was also obvious over Herrstedt, Bös, and Hargreaves.

M. Claim 24

> **24.** The method of claim 1, wherein said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are synergistically effective to antagonize NK_1 activity.

442. Claim 24 depends from claim 1 and further requires that palonosetron and netupitant are "synergistically effective to antagonize NK_1 activity." I see no definition of "synergistically effective to antagonize NK_1 activity" in the '826 patent, nor do I see disclosure of synergy in the specification. Any alleged synergistic effect is an inherent quality of palonosetron and netupitant being co-administered in therapeutic amounts. Patent applicant asserted as much during prosecution of the '050 application. EX1008 (file history of '050 application), 186 ("At ***all*** concentrations where the netupitant and palonosetron have an effect on the EC50 of substance P, they have a synergistic effect when combined."). As I described above, the combination of Herrstedt, Bös, and Hargreaves rendered obvious co-administering netupitant and palonosetron. *See* Section XV.A, above.

443. In addition to the inherency admission by the patentee before the Patent Office, recent studies also confirm any synergy is inherent to the co-administration that I've explained above was obvious. The literature reasons that "both netupitant and palonosetron can trigger NK_1 receptor internalization." EX1045 (Thomas), 2643; *see also id.*, 2642. Palonosetron—a 5-HT_3 receptor antagonist—affects NK_1 receptors "through a 5-HT_3 receptor-mediated effect" between the 5-HT_3 and NK_1 receptors. *Id.* The literature identifies this internalization as "***a mechanistic explanation of*** the additive and ***synergistic effects*** on the NK_1 receptor antagonism when a combination of netupitant and palonosetron is used in these cells." *Id*. (emphasis added); *see also* EX1041 (Rojas), 365, 368 (unlike other 5-HT_3 receptor antagonists, palonosetron triggered internalization of 5-HT_3 receptors, affecting the "5-HT3 and NK-1 receptor pathways in a dose- and time-dependent fashion"). These post-critical date publications identify the NK_1-receptor-internalization-property of palonosetron as a property intrinsic to that prior art 5-HT_3 receptor antagonist. Any alleged additive or synergistic effect on NK_1 receptor antagonism is thus inherent to the obvious combination of therapeutically-effective amounts of palonosetron and an NK_1 receptor antagonist.

444. Because the additive/synergistic effect is an inherent property that naturally results from administering therapeutically effective amounts of

palonosetron and an NK_1 receptor antagonist—a combination that Herrstedt teaches is favorable particularly for palonosetron's additional efficacy for treating delayed emesis—this allegedly unexpected result is merely an inherent property of a prior art or at least an obvious combination.

445. Accordingly, it is my opinion that claim 24 was obvious as a whole over Herrstedt, Bös, and Hargreaves.

N. Motivation to Combine

446. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the triple antiemetic combination therapy provided in Herrstedt, using therapeutically effective amounts of the new NK_1 and 5-HT_3 receptor antagonists as claimed. *See* Section XV.A, above. I described that persons having ordinary skill in the art would have had good reason to prophylactically treat (on Day 1, prior to chemotherapy) patients receiving highly and moderately emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt triple therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 and NK_1 receptor antagonists administered with dexamethasone on Day 1 (prior to chemotherapy) provided antiemetic effect). Additionally, I explained that a person having ordinary skill in the art would have

modified the Herrstedt triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron.

447. The person having ordinary skill in the art also would have modified the Herrstedt triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Section XV.A, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös explained the netupitant is administered orally (administration of oral doses as compared to intravenous has benefits as I described above) (*id.*, 19:2-38) and provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by

replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

448. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

449. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

O. Reasonable Expectation of Success

450. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in

modifying the Herrstedt triple active combination therapy with the claimed netupitant and palonosetron therapeutics. *See* Section XV.A, above. I explained, for example, that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome.

451. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would

have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant.

452. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XV.A, above.

453. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and Hargreaves to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XVI. ['826 PATENT GROUND 6] '826 PATENT CLAIMS 4-5 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND OPTIONALLY HERRINGTON.

454. For the reasons discussed in detail below, it is my opinion that claims 4-5 of the '826 patent were obvious as a whole. The obviousness of claims 4-5 is exemplified by disclosures in the Herrstedt, Bös, Hargreaves, and optionally Herrington references.

455. I have evaluated below whether the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses each and every element of each of claims 4-5 of the '826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a

reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 4

> **4.** The method of claim 1, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.

456. Claim 4 depends from independent claim 1 and additionally recites that only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days.

457. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. *See* Section XV.A, above.

458. Herrstedt discloses the NK_1 receptor antagonist is administered during the five day period. Herrstedt provides general dosing for 5 days following chemotherapy, as detailed above. Section XV.A. Herrstedt explains its aprepitant NK_1 receptor antagonist is administered on days one, two, and three:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3….

EX1010 (Herrstedt), 146.

459. Herrington discloses only one dose of NK_1 receptor antagonist is administered during said five days. Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. Herrington describes that:

> The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy….
>
> From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

EX1016 (Herrington), Background. A POSA thus would have understood that the single administration of an NK_1 receptor antagonist on day one was similarly effective to the dosing protocol of Herrstedt dosing the NK_1 receptor antagonist on multiple days. A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt's triple therapeutic combination for decreased costs, increased convenience, and patient preference for single administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would have had good reason to modify the dosing protocol of Herrstedt to only dose the NK_1 receptor antagonist on the first day (i.e., in a single dose) without dosing on subsequent days.

460. Additionally, as I explained above, the POSA had good reason to substitute Bös' netupitant for Herrstedt's aprepitant (Sections XV.A, XV.N, above), and netupitant was known to have a large half-life value, thus reducing any need for subsequent administrations of NK_1 receptor antagonist. It was known in the field that netupitant had a relatively long half-life value. EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). Accordingly, the POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination, if given as a single clinically effective dose within an hour of chemotherapy, would have sustained therapeutic efficacy over a 5-day period.

461. Accordingly, it is my opinion that claim 4 as a whole was also obvious over Herrstedt, Bös, and Hargreaves, and optionally in view of Herrington.

B. Claim 5

> **5.** The method of claim 1, wherein only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.

462. Claim 5 depends from independent claim 1 and additionally recites that only one dose of netupitant or a pharmaceutically acceptable salt thereof is administered during said five days, and said one dose is administered orally.

463. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. Furthermore, as I previously addressed above, it was obvious to administer the NK_1 receptor antagonist (e.g.,

netupitant) in only one pre-chemotherapy dose during the five day regimen. *See* Claim 4, above.

464. Bös supports administering only one dose of netupitant during said five days, and said one dose is administered orally. The POSA would have had good reason to orally administer netupitant because Bös describes excellent activity following oral administration. Bös explains in vivo testing with oral administration of netupitant provided good antagonist activity. EX1014 (Bös), 18:64-19:10 (gerbils), 19:11-20 (ferrets), 19:21-24 (Suncus murinus). Further, Bös teaches orally administering the family of NK_1 receptor antagonists—including netupitant—in a therapeutically effective dose:

> In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

Id., 42:5-11. It is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., about 10 to 1,000 mg) as a favorable starting point for identifying optimal oral therapeutic dose amounts for oral administration of netupitant. Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

465. Furthermore, the POSA had good reason to keep all administered therapeutics in the same form, such as for ease of use by administrator or patient. The POSA also would have preferred oral administration because oral administration was simpler, less costly, and more convenient and more preferred than intravenous administration. *See* Section XIII.A; EX1018 (Gralla), 2976. A POSA would have had good reason to therefore administer all the drugs in the antiemetic combination orally and would have had a reasonable expectation of success in administering them in this manner because the drugs, including netupitant, were known to have good oral activity. It is therefore my opinion that the POSA had good reason to prophylactically administer only one dose of netupitant during the five day period, where the one dose is administered orally, just prior to chemotherapy, with a reasonable expectation of success.

466. Accordingly, it is my opinion that claim 5 as a whole was also obvious over Herrstedt, Bös, and Hargreaves, and optionally in view of Herrington.

C. Motivation to Combine

467. As I explained above (Section XIII.A), persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy to orally administer the NK_1 receptor antagonist (netupitant) —as described in Bös and as claimed—because oral administration (e.g., with a

pill) was both simpler, less costly, and more convenient and more preferred than intravenous administration. *See* Section XIII.A; EX1018 (Gralla), 2976.

468. The skilled artisan also would have had good reason to modify the Herrstedt triple therapy to administer the NK_1 receptor antagonist (netupitant) on a single day (day one). Herrington explains there was no observed benefit in administering aprepitant on multiple consecutive days (i.e., days 1-3 of a chemotherapy treatment) as compared to administration of a single dose on only day one. EX1016 (Herrington), Abstract, 2083-2084. The person having ordinary skill in the art would have understood that decreasing the number of administrations of a therapeutic lowers costs, is preferred by patients, and provides additional ease of administration. *See* Section IX.G. The POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a ***more convenient single-day*** three-drug antiemetic regimen…."). Thus, the POSA would have had good reason to modify the Herrstedt protocol to use the Herrington oral administration of NK_1 receptor antagonist on a single day (i.e., day one).

D. Reasonable Expectation of Success

469. A POSA would have had a reasonable expectation of success in achieving a therapeutically effective result by modifying Herrstedt to administer

the NK_1 receptor antagonist netupitant orally on a single day (prophylactically, day one of a chemotherapy treatment). Herrington explains the single dose of NK_1 receptor antagonist aprepitant was just as effective as multiple doses of the aprepitant, yielding similar overall therapeutic effect including anti-nausea treatment. EX1016 (Herrington), 2083-2084. Because Herrington shows similar results with a single dose of aprepitant, the POSA would have had a reasonable expectation of success in providing similar therapeutic effect with the single netupitant dose. Additionally, the POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a ***more convenient single-day*** three-drug antiemetic regimen…."). A POSA would have had a reasonable expectation that netupitant would perform in the same manner because it was known that netupitant acted through the same mechanism to provide the same therapeutic effect and because netupitant was known to have a longer half-life. *See, e.g.*, EX1014 (Bös), 19:3-38. Such properties could further be readily confirmed via the PET studies described by Hargreaves.

470. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Hargreaves, and optionally Herrington to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XVII. [’826 PATENT GROUND 7] ’826 PATENT CLAIMS 10-14 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND OPTIONALLY ALOXI

471. For the reasons discussed in detail below, it is my opinion that claims 10-14 of the ’826 patent were obvious as a whole. The obviousness of claims 10-14 is exemplified by disclosures in the Herrstedt, Bös, Hargreaves, and optionally Aloxi references.

472. I have evaluated below whether the combination of Herrstedt, Bös, Hargreaves, and optionally Aloxi discloses each and every element of each of claims 10-14 of the ’826 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal “yes.”

A. Claim 10

> **10.** The method of claim 1, wherein said therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

473. Claim 10 additionally recites that the therapeutically effective amount of palonosetron or pharmaceutically acceptable salt thereof is from about 0.25 to about 0.75 mg based on the weight of the free base.

474. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. Section XV.A.

475. Herrstedt discloses that the therapeutically effective amount (clinical dose) of palonosetron is within the range of about 0.25 to about 0.75 mg based on the weight of the free base. Herrstedt discloses, in Table 3, that it was known in the art to administer palonosetron in a 0.25 mg intravenous dose.

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

EX1010 (Herrstedt), Table 3.

476. Aloxi confirms that a POSA had good reason to employ a dose from 0.25 mg to 0.75 mg of the free base of palonosetron. *See generally* Aloxi (testing 0.25 mg, 0.5 mg, and 0.75 mg palonosetron). Aloxi teaches palonosetron HCl capsules available and approved by the FDA for antiemetic treatment containing 0.56 mg palonosetron HCl, corresponding with 0.50 mg of the free base of palonosetron. EX1015 (Aloxi), 3. Aloxi thus explicitly discloses palonosetron dose squarely in the center of the claimed range from the range of 0.25 mg to 0.75 mg based on the weight of the free base.

477. Accordingly, it is my opinion that claim 10 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Aloxi.

B. Claim 11

> **11.** The method of claim 1, wherein said palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

478. Claim 11 additionally recites that the palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base.

479. I have previously addressed above that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. I have also explained that the palonosetron dosing range from about 0.25 mg to about 0.75 mg was obvious over the reference combination, optionally in view of Aloxi. *See* Claim 10, above.

480. Aloxi discloses palonosetron is administered as palonosetron hydrochloride, and said therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as free base. Aloxi capsules contained 0.56 mg palonosetron HCl (corresponding to 0.5 mg of palonosetron free base) formulated for oral administration and indicated for the prevention of acute nausea and vomiting following initial and repeat courses of moderately emetogenic chemotherapy. EX1015 (Aloxi), 1-4; *id.*, 3 (“Each light beige opaque soft gelatin

ALOXI Capsule ***contains 0.56 mg of palonosetron HCl*** equivalent to palonosetron 0.5 mg."). A POSA would have had good reason to use the FDA approved palonosetron HCl dose (0.56 mg) as the therapeutically effective amount of palonosetron administered to the patient. The POSA also would have had a reasonable expectation of success in achieving the desired therapeutic result by administering this known and approved therapeutic amount because the specific dose had gone through the rigors of FDA approval.

481. I also note that the '826 patent itself does not ascribe any particular or unexpected results associated with the 0.56 mg dose of palonosetron hydrochloride. I have reviewed the '826 patent and do not observe any particular benefits linked with a 0.56 mg dose of palonosetron HCl specifically. For example, the specification explains that 0.5 mg of palonosetron was selected for inclusion into a formulation, and that the 0.56 mg of palonosetron corresponded with 0.5 mg free base, but does not explain this dose of palonosetron to be better than any others. EX1001 ('826 patent), 13:60-14:29. Therefore, based on my review of the '826 patent, there is no particular or unexpected benefit ascribed specifically to the 0.56 mg dose of palonosetron hydrochloride.

482. Accordingly, it is my opinion that claim 11 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Aloxi.

C. Claim 12

12. The method of claim 1, wherein said palonosetron is administered orally.

483. Claim 12 additionally recites that the palonosetron is administered orally.

484. I have previously addressed above that claim 1 is obvious over Herrstedt, Bös, and Hargreaves.

485. Aloxi teaches said palonosetron is administered orally. Aloxi discloses that palonosetron HCl had been approved for treatment of CINV in an oral capsule formulation. EX1015 (Aloxi), 1, 4. Orally administered palonosetron HCl had near equivalency to intravenously administered palonosetron. *Id.* ("Efficacy was based on demonstrating non-inferiority of oral palonosetron doses compared to the approved I.V. formulation…. [F]or the 24 to 120 hour time period, non-inferiority was not shown."). The POSA would have had a reasonable expectation of success in achieving the therapeutic effect using the FDA-approved orally administered palonosetron HCl of Aloxi in Herrstedt's triple therapy combination.

486. As I explained previously, it is my opinion that there is good reason to keep all administered therapeutics in a drug combination in the same form, such as for ease of use by administrator or patient. Additionally, the POSA would have preferred oral administration to avoid patient discomfort associated with

intravenous injections and improve patient outlook on antiemetic efficacy. *See* Claim 5, above. A POSA would have had good reason to therefore administer all the drugs in the antiemetic drug combination orally and would have had a reasonable expectation of success in administering them in this manner because the drugs were known to have good oral activity and in some cases had FDA approval for oral administration.

487. Accordingly, it is my opinion that claim 12 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Aloxi.

D. Claim 13

The method of claim 1, comprising orally administering:
a) about 300 mg of netupitant as a free base on day one;
b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and
c) about 12 mg of dexamethasone on day one.

488. Claim 13 depends from claim 1 and additionally recites orally administering: a) about 300 mg of netupitant as a free base on day one; b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one; and c) about 12 mg of dexamethasone on day one.

489. I have previously addressed (Section XV.A, above) that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves.

490. As explained above, Bös discloses orally administering about 300 mg of netupitant as a free base. Bös describes oral administration of NK_1 receptor antagonists including netupitant in a dose range including 300 mg of netupitant as a free base. *See* Sections XV.D-XV.E (Claims 6-7). Herrstedt explains that in each of its clinical studies evaluating the triple combination therapy, the NK_1 receptor antagonist is administered on day one. EX1010 (Herrstedt), 146. The POSA likewise would have had good reason to prophylactically administer Bös' netupitant on day one in Herrstedt's therapy so the therapeutic agent could begin to take effect prior to administration of the emetogenic chemotherapy. Such dosing protocol was consistent with other NK_1 receptor antagonists. EX1010 (Herrstedt), 146.

491. Additionally, as explained above, the combination of Herrstedt, Bös, Hargreaves, and optionally Aloxi render obvious orally administering palonosetron (Claim 12) in a dose of about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base (Claims 10-11).

492. Herrstedt discloses orally administering dexamethasone in conjunction with administering the NK_1 receptor antagonist and 5-HT_3 receptor antagonist. Herrstedt provides a summary of two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, Section XV.A. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli

study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that in Herrstedt, 12 mg dexamethasone was orally administered on day one. Poli-Bigelli and Hesketh both expressly confirm 12 mg dexamethasone was orally administered on day one. Poli-Bigelli administers, for the regimen using NK_1 receptor antagonist, "oral dexamethasone 12 mg on Day 1." EX1039 (Poli-Bigelli), 3091. Likewise, Hesketh administers, for its regimen using NK_1 receptor antagonist, "oral dexamethasone 12 mg on day 1." EX1037 (Hesketh), 4113. Thus, a POSA would have had good reason to orally administer about 12 mg of dexamethasone on day one, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

493. Accordingly, it is my opinion that claim 13 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Aloxi.

E. Claim 14

14. The method of claim 1, comprising orally administering:
a) about 300 mg of netupitant as a free base on day one;
b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on day one;
c) about 12 mg of dexamethasone on day one; and
d) about 8 mg of dexamethasone on days two, three and four.

494. Claim 14 additionally recites orally administering: a) about 300 mg of netupitant as a free base on day one; b) about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.5 mg of palonosetron as a free base, on

day one; c) about 12 mg of dexamethasone on day one; and d) about 8 mg of dexamethasone on days two, three and four.

495. I have previously addressed (Section XV.A, above) that claim 1 was obvious over the combination of Herrstedt, Bös, and Hargreaves. Further, there is substantial overlap between Claims 13 and 14. Each of claim limitations 14(a), 14(b), and 14(c) are identical to corresponding claim limitations 13(a), 13(b), and 13(c). Accordingly, it is my opinion that each of these claim limitations was obvious for the same reasons as described above. *See* Claim 13, above.

496. Claim 14 further requires orally administering about 8 mg of dexamethasone on days two, three and four.

497. Herrstedt discloses orally administering dexamethasone in conjunction with administering the NK_1 receptor antagonist and 5-HT_3 receptor antagonist. As described above, Herrstedt summarizes two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, Section XV.A. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that in Herrstedt, 8 mg dexamethasone was orally administered on days two, three and four. Poli-Bigelli and Hesketh both expressly confirm 8 mg dexamethasone was orally administered on days two, three and four. Poli-Bigelli administers, for the regimen using NK_1 receptor antagonist,

"oral dexamethasone 8 mg once daily on Days 2 and 3; and oral dexamethasone 8 mg on Day 4." EX1039 (Poli-Bigelli), 3091. Likewise, Hesketh administers, for its regimen using NK_1 receptor antagonist, "oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4." EX1037 (Hesketh), 4113. Thus, a POSA would have had good reason to orally administer about 8 mg of dexamethasone on days two, three and four, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

498. Accordingly, it is my opinion that claim 14 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Aloxi.

F. Motivation to Combine

499. As I explained above (Sections XV.A, XV.N), persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

500. The persons having ordinary skill in the art also would have been motivated to administer palonosetron in an FDA-approved oral formulation. Aloxi describes an FDA-approved oral capsule of palonosetron HCl that was shown to provide antiemetic effect when administered to patients receiving emetogenic

chemotherapy. EX1015 (Aloxi), 2-4. Thus, the POSA would have had good reason to use the Aloxi capsule of palonosetron HCl for its administration of palonosetron.

G. Reasonable Expectation of Success

501. As I explained above (Sections XV.A, XV.O), persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome. Similarly, I explained above that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. Section XV.A, above.

502. The POSA also would have had a reasonable expectation of success in using the palonosetron HCl capsules of Aloxi to administer the Herrstedt palonosetron. Aloxi explains the orally administered palonosetron HCl capsules were as efficacious as the previously-FDA-approved intravenous formulation. EX1015 (Aloxi), 4 (non-inferiority studies). Additionally, Aloxi provides clinical studies showing the 0.56 mg palonosetron HCl capsules were therapeutically effective in treating CINV, leading to FDA approval for prophylaxis with

emetogenic chemotherapy. *Id.*, 2, 4. Therefore, the POSA would have had a reasonable expectation of success that Aloxi's palonosetron HCl capsules would treat CINV when incorporated into the Herrstedt study.

503. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Hargreaves, and optionally Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XVIII. ['515 PATENT GROUND 1] '515 PATENT CLAIMS 11-17 AND 19-23 WERE OBVIOUS OVER HERRSTEDT, BÖS, AND OPTIONALLY HERRINGTON

504. For the reasons discussed in detail below, it is my opinion that each of claims 11-17 and 19-23 of the '515 patent was obvious as a whole. The obviousness of claims 11-17 and 19-23 is exemplified by disclosures in the Herrstedt, Bös, and optionally Herrington references.

505. I have evaluated below whether the combination of Herrstedt, Bös, and optionally Herrington discloses each and every element of each of claims 11-17 and 19-23 of the '515 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

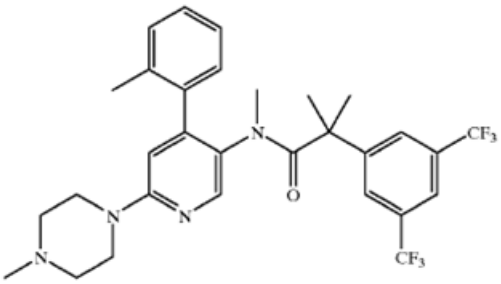
506. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010 (Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt also discloses administering to the patient on day one a first dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146.

507. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

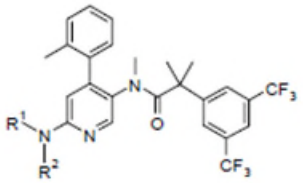
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

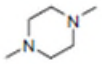
EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*,

17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the combination treatment disclosed in Herrstedt.

508. Herrington discloses administration of NK_1 receptor antagonist (aprepitant) on day one—and only on day one—of a five-day treatment period was effective at preventing nausea and vomiting from chemotherapy-induced emesis. EX1016 (Herrington), Abstract. Herrington identified "no statistically significant differences" between patients treated with a single 125-mg dose of aprepitant and

patients receiving "the traditional 3-day regimen" of the NK_1 receptor antagonist. *Id.*, 2084 & Fig. 2.

509. The sections below explain in more detail how Herrstedt, Bös, and optionally Herrington disclose each and every element of claims 11-17 and 19-23. I first analyze independent claim 11 of the challenged '515 patent. Thereafter, I analyze dependent claims 12-17 and 19-23.

A. Claim 11

11[pre]. A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising

510. I have reproduced above the preamble of claim 11 of the '515 patent. Herrstedt teaches a "method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof" as disclosed in the preamble of claim 11. For example, Herrstedt teaches methods for prophylactically treating "[c]hemotherapy-induced ***nausea and vomiting***" in a patient. EX1010 (Herrstedt), 143. Herrstedt explains that chemotherapy is an emesis-inducing event. *Id.* ("emesis is a natural consequence of treatment with most cancer chemotherapy."). Herrstedt describes its primary therapeutic endpoint was no emesis for a period of five consecutive days following administration of the chemotherapeutic agent (e.g., five days "postcisplatin"). *Id.*, 146 ("Complete response, defined as 'no emesis and no rescue therapy on days 1–5

postcisplatin', was the primary end-point in all studies."). Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in the preamble of claim 1.

> **11(a).** administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis,

511. I have reproduced above the administering step (a) element of claim 11. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the administering step of claim 11(a).

512. Herrstedt expressly discloses multiple studies for treatment of highly-emetogenic chemotherapy in patients with a triple-drug combination administered to patients including an NK_1 receptor antagonist (aprepitant). EX1010 (Herrstedt), 146 ("Two of the HEC studies used an identical design…ondansetron, dexamethasone and ***aprepitant*** day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes the NK_1 receptor antagonist is administered in a therapeutically effective amount, providing benefits to patients receiving the antiemetic combination. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.").

513. Herrstedt discloses the therapeutically effective amount of NK_1 receptor antagonist is effective to treat nausea and vomiting during the acute and delayed phases of emesis. Herrstedt's NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed*** emesis." EX1010 (Herrstedt), Abstract. Summarizing MASCC guidelines, Herrstedt identifies use of an NK_1 receptor antagonist (aprepitant) as effective to treat nausea and vomiting during the acute and delayed phases. EX1010 (Herrstedt), 148-149 & Table 4 (reproduced below).

Table 4.

Summary of the recommendations in the MASCC guidelines [2].

Prophylaxis of acute nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Serotonin antagonist + dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Serotonin antagonist + dexamethasone + aprepitant
Moderate (other than AC)	Serotonin antagonist + dexamethasone
Low	Dexamethasone
Minimal	No routine prophylaxis
Prophylaxis of delayed nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Aprepitant or dexamethasone
Moderate (other than AC)	Dexamethasone, a serotonin antagonist may be used as an alternative
Low	No routine prophylaxis
Minimal	No routine prophylaxis

*Recommended doses of anti-emetics are given in reference [48].

Herrstedt describes studies treating nausea and vomiting with a therapeutically effective amount of the NK_1 receptor antagonist and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

514. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt treated nausea and vomiting during the acute and delayed phases of emesis. For example, Herrstedt describes its combination therapy provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the dosing combination treats of nausea and vomiting in response to chemotherapy during ***both the acute phase and the delayed phase***. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096.

515. Hesketh also confirms the dosing combination of Herrstedt treats nausea and vomiting in response to chemotherapy during ***both the acute phase and the delayed phase***. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

516. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48.

Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

517. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The ***effective amount*** for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches administering from a dosing range of about 10 to 1,000 mg for a therapeutically effective amount.

518. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with

Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high

likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism). Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, and would have had a reasonable expectation of success that such administration with a therapeutically effective amount of netupitant would be effective to treat nausea and vomiting during the acute and delayed phases of emesis.

519. Accordingly, Herrstedt discloses administering to said patient an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of netupitant for treatment of nausea and vomiting during the acute and delayed phases of emesis, such as in the method disclosed in Herrstedt. Thus, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 11(a).

> **11(b).** wherein said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive

> days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said nausea and vomiting for said five consecutive days.

520. I have reproduced above the netupitant dose (b) element of claim 11. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the netupitant dose of claim 11(b).

521. Herrstedt discloses a single dose of NK_1 receptor antagonist is administered on day one of said five consecutive days. Herrstedt explains its aprepitant NK_1 receptor antagonist is administered on days one, two, and three:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3….

EX1010 (Herrstedt), 146. Herrstedt explains that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that a single dose of its NK_1 receptor antagonist is administered on day one. Poli-Bigelli confirms the dosing combination included a single dose of aprepitant on day one of the five consecutive day study. EX1039 (Poli-Bigelli), 3091 ("The aprepitant regimen consisted of ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg ***on Day 1***…."); *id.*, Abstract (evaluating results "during the

5-day period post-cisplatin"; evaluation of patients "[d]uring the 5 days after chemotherapy"). Hesketh likewise confirms the dosing combination included a single dose of aprepitant on day one of the five consecutive day study. EX1037 (Hesketh), 4113 ("Patients in the aprepitant group received ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg ***on day 1***…."); *id.*, Abstract (evaluation of patient response "on days 1 to 5" after chemotherapy). A POSA would have known orally administered aprepitant was available in capsules of either 40 mg, 80 mg, or 125 mg; thus the orally administered 125 mg dose of aprepitant administered on day one in Poli-Bigelli, Hesketh, and thus as summarized in Herrstedt, was a single dose of the NK_1 receptor antagonist. EX1030 (Emend label), 1; EX1031 (Archived Emend label), 1.

522. The combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of said five consecutive days, no further netupitant is administered during said five consecutive days, and the single dose of netupitant is effective to treat said nausea and vomiting for said five consecutive days. Herrstedt describes administering aprepitant on days one, two, and three of the five consecutive days. EX1010 (Herrstedt), 146. But as I explained above (Claim element 11(a)), the POSA had good reason to substitute Bös' netupitant for Herrstedt's aprepitant. Netupitant was known to have a large half-life value, thus reducing any need for subsequent administrations of NK_1 receptor antagonist.

EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). The POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination provided further reason to omit subsequent doses of NK_1 receptor antagonist because a single dose would sustain therapeutic efficacy. In other words, the POSA would have understood a single day one dose of netupitant to be effective to treat nausea and vomiting for the five consecutive days. Thus, the combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of said five consecutive days, no further netupitant is administered during said five consecutive days, and said single dose of netupitant is effective to treat said nausea and vomiting for said five consecutive days.

523. Herrington confirms a single dose of NK_1 receptor antagonist administered on day one of said five consecutive days, where no further NK_1 receptor antagonist is administered during said five consecutive days, is effective to treat nausea and vomiting for the five consecutive days. Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. Herrington describes that:

> The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy….
>
> From this pilot study of patients who were receiving palonosetron,

> aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

EX1016 (Herrington), Background. A POSA thus would have understood that the single administration of an NK_1 receptor antagonist on day one was similarly effective to the dosing protocol of Herrstedt dosing the NK_1 receptor antagonist on multiple days. Herrington reports this efficacy (to treat said nausea and vomiting) was evaluated across the entire five day period. EX1016 (Herrington), 2081 ("The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy."). Herrington reports the single day one dose of NK_1 receptor antagonist is effective to treat said nausea and vomiting for said five consecutive days:

> There were no significant differences between Arms A [3-day aprepitant] and B [single day one dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In ***Arms*** A and ***B, 93% of patients were emesis-free from Days 1-5*** compared with only 50% in Arm C [control group].

EX1016 (Herrington), Abstract. Herrington describes that the single day one dose of NK_1 receptor antagonist provided control against nausea across the five day period. *Id.*, 2086 ("The control of nausea was achieved in similar fashion between the 2 aprepitant arms."). Although Herrington identified "a trend toward better significant nausea on Days 4-5 with the 3-day Arm A versus the single dose" the

mean severity of nausea for the single dose of aprepitant was lower than the control test group across all five days. *Id.*, 2086, 2084 & Table 4 (reproduced below).

TABLE 4
Severity of Nausea Using VAS

	Severity of nausea using VAS (mean±SD; median, range)			
	Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	*P**	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0–95)	8.7 ± 15.7 0(0–60)	.82	15.6 ± 32.1 0(0–95)
Day 2	15.2 ± 24.6 4(0–95)	11.0 ± 16.1 1(0–50)	.80	28.4 ± 39.2 2.5(0–100)
Day 3	15.0 ± 26.1 1.5(0–95)	12.3 ± 16.5 2.5(0–50)	.95	30.3 ± 40.4 2.5(0–100)
Day 4	10.5 ± 21.8 3.5(0–95)	16.6 ± 23.6 2.5(0–75)	.62	19.6 ± 31.5 2.5(0–95)
Day 5	12.0 ± 25.2 0(0–95)	18.3 ± 27.2 0(0–80)	.52	20.6 ± 34.0 0(0–95)

VAS indicates visual analog scale; SD, standard deviation.
* Wilcoxon 2-sample test, (3-Day vs 1-Day).

Thus, Herrington confirms its single dose of aprepitant administered on day one, where no further NK_1 receptor antagonist is administered during the five day period, is effective to treat nausea and vomiting for the five consecutive days.

524. A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt's triple therapeutic combination for decreased costs, increased convenience, and patient preference for single administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would

have had good reason to employ the single dose of NK_1 receptor antagonist in the dosing protocol of Herrstedt without dosing on subsequent days. As discussed above, the POSA would have employed Bös' second generation NK_1 receptor antagonist—netupitant—in Herrstedt's protocol.

525. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 11(b).

526. The combination of Herrstedt, Bös, and optionally Herrington thus teaches all of the elements of claim 11 and rendered the claim obvious as a whole.

B. Claim 12

> **12.** The method of claim 11, comprising orally administering from about 200 to about 400 mg of netupitant as the free base.

527. Claim 12 depends from independent claim 11 and additionally recites orally administering from about 200 to about 400 mg of netupitant as the free base.

528. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

529. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—in a range that includes from about 200 mg to about 400 mg as the free base. Bös discloses a family of NK_1 receptor antagonists including netupitant are useful for treating chemotherapy-induced emesis. EX1014 (Bös), 2:1-65, 14:9-20. Bös discloses an oral

administration dose range for its NK_1 receptor antagonists (including netupitant) that encompasses the claimed range from about 200 to about 400 mg. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

530. Bös explicitly recognizes the application of its NK_1 receptor antagonists "for treatment induced vomiting" including "the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist." *Id.*, 1:60-64. Bös describes netupitant and its synthesis (*id.*, 14:9-15:20 (Formula Ib is netupitant)) and explains that netupitant "is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)" (*id.*, 14:32-38). *See also id.*, 18:42-19:38 (favorable in vitro and in vivo studies as well as oral bioavailability and half-life results).

531. It is my opinion that a POSA would have recognized Bös' range spanning two orders of magnitude (about 10 to 1,000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts. It is my opinion that the

POSA would have had good reason to optimize Bös' range when determining the therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22; Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect orally administering that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

532. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '515 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '515 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1003 ('515 patent), 8:13-19. Therefore, the '515 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based

on common factors. The POSA therefore would have found it routine to arrive at the 200-400 mg oral therapeutic dose range of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a range including from about 200 to about 400 mg when determining the amount of netupitant to orally administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

533. Accordingly, it is my opinion that claim 12 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

C. Claim 13

> **13.** The method of claim 11, comprising orally administering about 300 mg of netupitant as the free base.

534. Claim 13 depends from independent claim 11 and additionally recites orally administering about 300 mg of netupitant as the free base.

535. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

536. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be

appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

537. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, and optionally Herrington to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA

would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating nausea and vomiting.

538. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '515 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '515 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1003 ('515 patent), 8:13-19. Therefore, the '515 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to orally administer to the

patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

539. The ’515 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’515 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1003 (’515 patent), 16:34-17:2) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1003 (’515 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 17:4-29), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’515 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

540. Accordingly, it is my opinion that claim 13 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

D. Claim 14

14. The method of claim 11, wherein when said emesis inducing event comprises highly emetic chemotherapy, and the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

541. Claim 14 depends from independent claim 11 and additionally recites that said emesis inducing event comprises highly emetic chemotherapy, and the chemotherapy is selected from the group consisting of carmustine, ***cisplatin***, cyclophosphamide≥1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

542. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

543. Herrstedt discloses the emesis inducing event comprises highly emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including highly emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly*** or moderately ***emetogenic chemotherapy***").

544. Herrstedt also discloses its antiemetic drug combination is administered to treat the emesis inducing event of highly emetic chemotherapy where the chemotherapy is, for example, ***cisplatin***. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described above in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

545. Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a $serotonin_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such highly emetogenic chemotherapy includes cisplatin, mechloretamine, streptozocin, dacarbazine, and cyclophosphamide > 1500 mg/m^2. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the emesis inducing event of highly emetic chemotherapy where the chemotherapy is any one of cisplatin, mechloretamine, streptozocin, dacarbazine, and cyclophosphamide > 1500 mg/m^2, or a combination thereof.

546. Accordingly, it is my opinion that claim 14 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

E. Claim 15

> **15.** The method of claim 11, wherein when said emesis inducing event comprises moderately emetic chemotherapy, and the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

547. Claim 15 depends from independent claim 11 and additionally recites that said emesis inducing event comprises moderately emetic chemotherapy, and the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

548. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

549. Herrstedt suggests the emesis inducing event comprises moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

550. Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the emesis inducing event comprises highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy includes carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1000 mg/m^2 (which includes

cytarabine>1 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

It would have been within a POSA's skill and abilities to apply Herrstedt's combination therapy for treating a highly or moderately emetogenic chemotherapy, such as any of those listed in Table 1. Because the '515 patent does not provide details for implementing its administration for the claimed chemotherapy agents, this further confirms it was within the skills of the POSA to do so. Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the emesis inducing event of moderately emetic chemotherapy where the chemotherapy is any one of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1000 mg/m^2 (which includes

cytarabine>1 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin, or a combination thereof.

551. Accordingly, it is my opinion that claim 15 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

F. Claim 16

> **16.** The method of claim 11, wherein said emesis inducing event comprises chemotherapy selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

552. Claim 16 depends from independent claim 11 and additionally recites that said emesis inducing event comprises chemotherapy selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

553. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

554. Herrstedt discloses the emesis inducing event comprises chemotherapy including cisplatin. Herrstedt discloses its antiemetic drug combination is administered to treat the emesis inducing event of highly or

moderately emetic chemotherapy. More specifically, Herrstedt summarizes examples where the chemotherapy is ***cisplatin***. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based***, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described above in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

555. Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a $serotonin_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such highly or moderately emetogenic chemotherapy includes carboplatin, cyclophosphamide, cytarabine>1 mg/m^2 (e.g., cytarabine>1000 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, cisplatin, dacarbazine, mechlorethamine, and streptozotocin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the emesis inducing event comprising chemotherapy, where the chemotherapy is any one of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, cisplatin, dacarbazine, mechlorethamine, and streptozotocin, or a combination thereof.

556. Accordingly, it is my opinion that claim 16 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

G. Claim 17

17. The method of claim 11, for the treatment of CINV defined as no emetic episodes and no use of rescue medication following chemotherapy.

557. Claim 17 depends from independent claim 11 and additionally recites for the treatment of CINV defined as no emetic episodes and no use of rescue medication following chemotherapy.

558. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

559. As an initial matter, I understand that independent claim 11 does not recite anything for the "treatment of CINV." Instead, claim 11 more broadly concerns treatment of nausea and vomiting during the acute and delayed phases of emesis, without limiting it to chemotherapy-induced nausea and vomiting (CINV). Nonetheless, regardless of whether claim 17 requires ***treatment of CINV*** to be defined as no emetic episodes and no use of rescue medication following chemotherapy or more broadly ***treatment of nausea and vomiting*** to be defined as no emetic episodes and no use of rescue medication following chemotherapy, this claim is obvious in view of the combination of Herrstedt, Bös, and optionally Herrington.

560. Herrstedt defines treatment of nausea and vomiting—and more specifically of chemotherapy-induced nausea and vomiting—as no emetic episodes and no use of rescue medication following chemotherapy. Herrstedt explains that, following chemotherapy, "[c]omplete response, ***defined as 'no emesis and no***

rescue therapy on days 1-5 postcisplatin', was the ***primary end-point in all studies***." EX1010 (Herrstedt), 146. Herrstedt explains that the "complete response" includes both patients "with ***no emesis***" (i.e., no emetic episodes) and "without the need of ***rescue anti-emetics***" (i.e., no use of rescue medication). *Id.*

561. As I explained above (Section XVIII.A, Claim 11) Herrstedt describes studies treating nausea and vomiting with a therapeutically effective amount of the NK_1 receptor antagonist and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. Poli-Bigelli expressly confirms that Herrstedt's treatment of nausea and vomiting (e.g., CINV) is defined as no emetic episodes and no use of rescue medication following chemotherapy. EX1039 (Poli-Bigelli), 3092 (following chemotherapy, the "proportion of patients who achieved a complete response (defined as ***no emetic episodes and no use of rescue therapy***) in the overall study period (Days 1-5) was ***the primary endpoint of the efficacy analysis***."). Hesketh also confirms that Herrstedt's treatment of nausea and vomiting (e.g., CINV) is defined as no emetic episodes and no use of rescue medication following chemotherapy. EX1037 (Hesketh), 4113 ("The ***primary end point for the efficacy analysis*** was the proportion of patients with complete response, ***defined as no emetic episodes and no rescue therapy*** (ie ***medication*** taken for established nausea or vomiting) overall (day 1 to 5)" after chemotherapy).

562. Accordingly, it is my opinion that claim 17 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

H. Claim 19

> **19.** The method of claim 11, wherein said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

563. Claim 19 depends from independent claim 11 and additionally recites said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

564. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

565. Herrstedt discloses a regimen for treating nausea and vomiting wherein the emesis inducing event is highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"). Herrstedt discloses its NK_1 antiemetic combination provides therapeutic effect for "emesis induced by highly or moderately emetogenic chemotherapy" noting in particular that the NK_1 receptor antagonist is "also active in the protection against delayed emesis." *Id.*, Abstract. Herrstedt further discloses that the administration details are

provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

566. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was used to treat nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy, and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id*. ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (i.e., cisplatin) and is effective to prevent or reduce the severity of

nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

567. Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, and would have had a reasonable expectation of success that such dosing would treat nausea and vomiting wherein the emesis inducing event is highly emetogenic chemotherapy (e.g., cisplatin) and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

568. Accordingly, it is my opinion that claim 19 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

I. Claim 20

20. The method of claim 11, wherein said emesis inducing event is moderately emetogenic chemotherapy, and said regimen is effective

to prevent or reduce the severity of nausea during the acute and delayed phases.

569. Claim 19 depends from independent claim 11 and additionally recites said emesis inducing event is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

570. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

571. Herrstedt suggests the emesis inducing event comprises moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

572. Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist

"increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

It would have been within a POSA's skill and abilities to apply Herrstedt's combination therapy for treating a highly or moderately emetogenic chemotherapy, such as any of those listed in Table 1. Because the '515 patent does not provide an example for implementing its administration MEC, this further confirms it was within the skills of the POSA to do so. Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the emesis inducing event of moderately emetogenic chemotherapy.

573. Herrstedt discloses its NK_1 antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

574. A POSA reviewing Herrstedt would have understood that the antiemetic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to emetogenic chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during both the

acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

575. Each of Poli-Bigelli and Hesketh describe the NK_1 receptor antagonist dosing regimen is useful for preventing or reducing the severity of nausea where chemotherapy is cisplatin (highly emetogenic chemotherapy). Nonetheless, a POSA would have reasonably expected similar anti-nausea effect for treatment of nausea where the chemotherapy is moderately emetogenic because the mechanism of treatment is the same (e.g., occupancy of NK_1 receptors). Herrstedt confirms that its regimen is applicable for treating both highly emetogenic and moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract.

576. Therefore, a POSA would have had good reason to prophylactically administer the drug regimen of Herrstedt, employing netupitant from Bös, and would have had a reasonable expectation of success that such dosing would treat

nausea and vomiting wherein the emesis inducing event is moderately emetogenic chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

577. Accordingly, it is my opinion that claim 19 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

J. Claims 21-22

> **21.** The method of claim 11, wherein said emesis inducing event comprises cisplatin.
>
> **22.** The method of claim 11, wherein said emesis inducing event comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

578. Each of claims 21 and 22 depends from independent claim 11 and additionally recites that said emesis inducing event comprises cisplatin (claim 21) or comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 22).

579. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

580. Herrstedt discloses the emesis inducing event comprises cisplatin. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

581. Additionally, as I explained above, Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. EX1010 (Herrstedt), Abstract. Herrstedt suggests emesis inducing events include carboplatin, cisplatin, oxaliplatin, or doxorubicin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the emesis inducing event where said emesis inducing event comprises cisplatin (as in claim 21) and where said emesis inducing event comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (as in claim 22).

582. Accordingly, it is my opinion that each of claims 21-22 as a whole were also obvious over Herrstedt, Bös, and optionally Herrington.

K. Claim 23

23. The method of claim 11, wherein said emesis inducing event comprises cyclophosphamide.

583. Claim 23 depends from independent claim 11 and additionally recites that said emesis inducing event comprises cyclophosphamide.

584. As I previously addressed above, claim 11 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.A, above.

585. Herrstedt discloses the emesis inducing event comprises highly or moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including highly or moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***"). Herrstedt identifies that the NK_1 receptor antagonist is broadly applicable to treating chemotherapy-induced nausea and vomiting.

586. Herrstedt describes cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

587. Thus, a POSA would have understood Herrstedt to suggest that its antiemetic drug combination is administered to treat the emesis inducing event of highly or moderately emetogenic chemotherapy where the chemotherapy is cyclophosphamide.

588. Accordingly, it is my opinion that claim 23 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

L. Motivation to Combine

589. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the antiemetic combination therapy provided in Herrstedt, using therapeutically effective amounts of the second generation NK_1 receptor antagonist as claimed. *See* Section XVIII.A, above. I

described that persons having ordinary skill in the art would have had good reason to prophylactically treat (on Day 1, prior to chemotherapy) patients receiving emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt antiemetic therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (NK_1 receptor antagonist administered with dexamethasone on Day 1 provided antiemetic effect).

590. The person having ordinary skill in the art also would have modified the Herrstedt antiemetic therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Section XVIII.A, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös explained the netupitant is

administered orally (administration of oral doses as compared to intravenous has benefits as I described above) (*id.*, 19:2-38) and provided a dosing range of about 10 to about 1000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

591. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt antiemetic combination therapy with Bös' second generation NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving emetogenic chemotherapy during the acute and delayed phases.

592. The skilled artisan also would have had good reason to modify the Herrstedt antiemetic therapy to administer Bös' NK_1 receptor antagonist (netupitant) on a single day (day one). Herrington explains there was no observed benefit in administering aprepitant on multiple consecutive days (i.e., days 1-3 of a chemotherapy treatment) as compared to administration of a single dose on only day one. EX1016 (Herrington), Abstract, 2083-2084. The person having ordinary skill in the art would have understood that decreasing the number of administrations of a therapeutic lowers costs, is preferred by patients, and provides additional ease of administration. *See* Section IX.G. The POSA would have

understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen…."). Thus, the POSA would have had good reason to modify the Herrstedt protocol to use the Herrington oral administration of NK_1 receptor antagonist on a single day (i.e., day one).

M. Reasonable Expectation of Success

593. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt antiemetic combination therapy with the claimed netupitant. A person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve a similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected

therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant.

594. A POSA would have had a reasonable expectation of success in achieving a therapeutically effective result by modifying Herrstedt to administer the NK_1 receptor antagonist netupitant orally on a single day (prophylactically, day one of a chemotherapy treatment). Herrington explains the single dose of NK_1 receptor antagonist aprepitant was just as effective as multiple doses of the aprepitant, yielding similar overall therapeutic effect including anti-nausea treatment. EX1016 (Herrington), 2083-2084. Because Herrington shows similar results with a single dose of aprepitant, the POSA would have had a reasonable expectation of success in providing similar therapeutic effect with the single netupitant dose. Additionally, the POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen…."). A POSA would have had a reasonable expectation that netupitant would perform in the same manner because it was known that netupitant acted through the same

mechanism to provide the same therapeutic effect and because netupitant was known to have a longer half-life. *See, e.g.*, EX1014 (Bös), 19:3-38.

595. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and optionally Herrington to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XIX. ['515 PATENT GROUND 2] '515 PATENT CLAIMS 1-10 AND 18 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND OPTIONALLY HERRINGTON

596. For the reasons discussed in detail below, it is my opinion that each of claims 1-10 and 18 of the '515 patent was obvious as a whole. The obviousness of claims 1-10 and 18 is exemplified by disclosures in the Herrstedt, Bös, Hargreaves, and optionally Herrington references.

597. I have evaluated below whether the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses each and every element of each of claims 1-10 and 18 of the '515 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

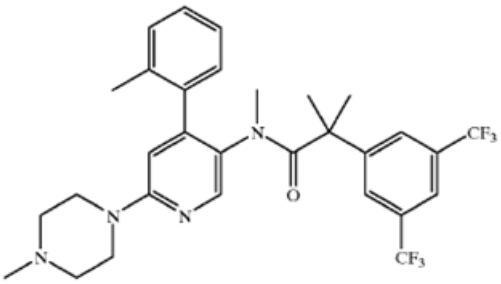
598. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010 (Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt also discloses administering to the patient on day one a first dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the 20 mg traditional day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146.

599. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

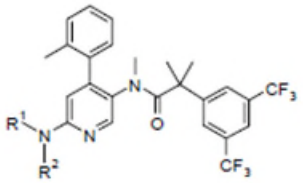
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

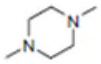
EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*,

17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the combination treatment disclosed in Herrstedt.

600. Hargreaves explains NK_1 receptor occupancy of greater than 75% is associated with therapeutic effectiveness. EX1012 (Hargreaves), Abstract, 23, Fig. 6B. Hargreaves also teaches to measure NK_1 receptor occupancy in the striatum. As I explain further below, a POSA would have understood the therapeutically effective dose of netupitant would likely occupy at least 70% of NK_1 receptors in the striatum 72 hours after administration.

601. Herrington discloses administration of NK_1 receptor antagonist (aprepitant) on day one—and only on day one—of a five-day treatment period was effective at preventing nausea and vomiting from chemotherapy-induced emesis. EX1016 (Herrington), Abstract. Herrington identified "no statistically significant differences" between patients treated with a single 125-mg dose of aprepitant and patients receiving "the traditional 3-day regimen" of the NK_1 receptor antagonist. *Id.*, 2084 & Fig. 2.

602. The sections below explain in more detail how Herrstedt, Bös, Hargreaves, and optionally Herrington disclose each and every element of claims 1-10 and 18. I first analyze independent claim 1 of the challenged '515 patent. Thereafter, I analyze dependent claims 2-10 and 18.

A. Claim 1

1[pre]. A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising

603. I have reproduced above the preamble of claim 1 of the '515 patent. Herrstedt teaches a "method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof" as disclosed in the preamble of claim 1. For example, Herrstedt teaches methods for prophylactically treating "[c]hemotherapy-induced ***nausea and vomiting***" in a patient. EX1010 (Herrstedt), 143. Herrstedt explains that chemotherapy is an

emesis-inducing event. *Id.* ("emesis is a natural consequence of treatment with most cancer chemotherapy."). Herrstedt describes its primary therapeutic endpoint was no emesis for a period of five consecutive days following administration of the chemotherapeutic agent (e.g., five days "postcisplatin"). *Id.*, 146 ("Complete response, defined as 'no emesis and no rescue therapy on days 1–5 postcisplatin', was the primary end-point in all studies."). Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in the preamble of claim 1.

> **1(a).** administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis,

604. I have reproduced above the administering step (a) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the administering step of claim 1(a).

605. Herrstedt expressly discloses multiple studies for treatment of highly-emetogenic chemotherapy in patients with a triple-drug combination administered to patients including an NK_1 receptor antagonist (aprepitant). EX1010 (Herrstedt), 146 ("Two of the HEC studies used an identical design…ondansetron, dexamethasone and ***aprepitant*** day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes the NK_1 receptor antagonist is administered in a therapeutically effective amount, providing benefits to patients

receiving the antiemetic combination. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.").

606. Herrstedt discloses the therapeutically effective amount of NK_1 receptor antagonist is effective to treat nausea and vomiting during the acute and delayed phases of emesis. Herrstedt's NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed*** emesis." EX1010 (Herrstedt), Abstract. Summarizing MASCC guidelines, Herrstedt identifies use of an NK_1 receptor antagonist (aprepitant) as effective to treat nausea and vomiting during the acute and delayed phases. EX1010 (Herrstedt), 148-149 & Table 4 (reproduced below).

Table 4.

Summary of the recommendations in the MASCC guidelines [2].

Prophylaxis of acute nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Serotonin antagonist + dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Serotonin antagonist + dexamethasone + aprepitant
Moderate (other than AC)	Serotonin antagonist + dexamethasone
Low	Dexamethasone
Minimal	No routine prophylaxis
Prophylaxis of delayed nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Aprepitant or dexamethasone
Moderate (other than AC)	Dexamethasone, a serotonin antagonist may be used as an alternative
Low	No routine prophylaxis
Minimal	No routine prophylaxis

*Recommended doses of anti-emetics are given in reference [48].

Herrstedt describes studies treating nausea and vomiting with a therapeutically effective amount of the NK_1 receptor antagonist and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

607. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt treated nausea and vomiting during the acute and delayed phases of emesis. For example, Herrstedt describes its combination therapy provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the dosing combination treats of nausea and vomiting in response to chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096.

608. Hesketh also confirms the dosing combination of Herrstedt treats nausea and vomiting in response to chemotherapy during ***both the acute phase and the delayed phase***. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

609. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil

and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

610. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The ***effective amount*** for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective dose.

611. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the

> regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism). Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, and would have had a reasonable expectation of success that such administration with a therapeutically effective amount of netupitant would be effective to treat nausea and vomiting during the acute and delayed phases of emesis.

612. Accordingly, Herrstedt discloses administering to said patient an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount which is

effective to treat nausea and vomiting during the acute and delayed phases of emesis, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of netupitant for treatment of nausea and vomiting during the acute and delayed phases of emesis, such as in the method disclosed in Herrstedt. Thus, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 1(a).

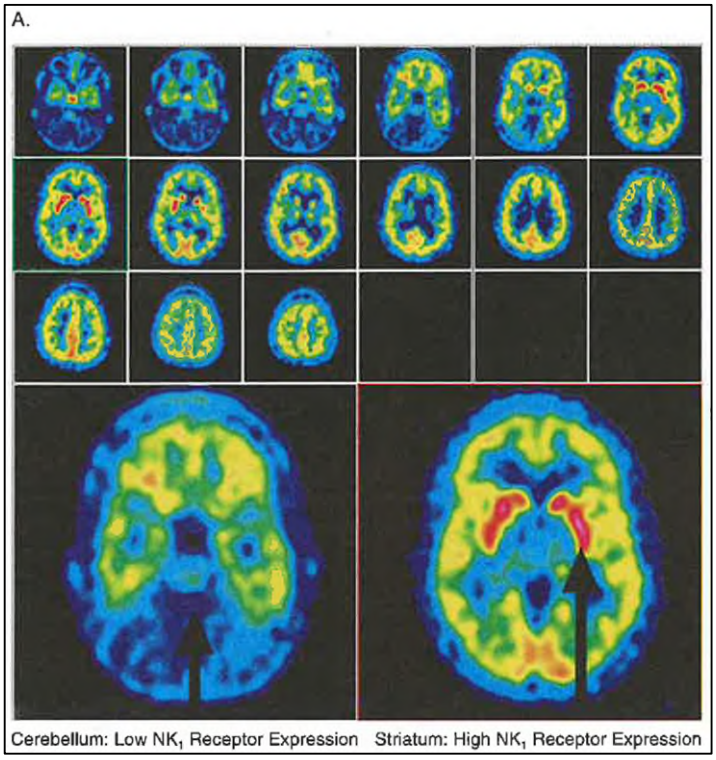
> **1(b).** and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK_1 receptors in the striatum seventy-two hours after said administration,

613. I have reproduced above the therapeutically effective amount (b) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the systemic circulation, crossing of the blood brain barrier, and occupancy of 70% or more of NK_1 receptors in the striatum seventy-two hours after administration of claim 1(b).

614. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of compounds that are administered orally. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"). Orally administered netupitant does not act locally at the place of

administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

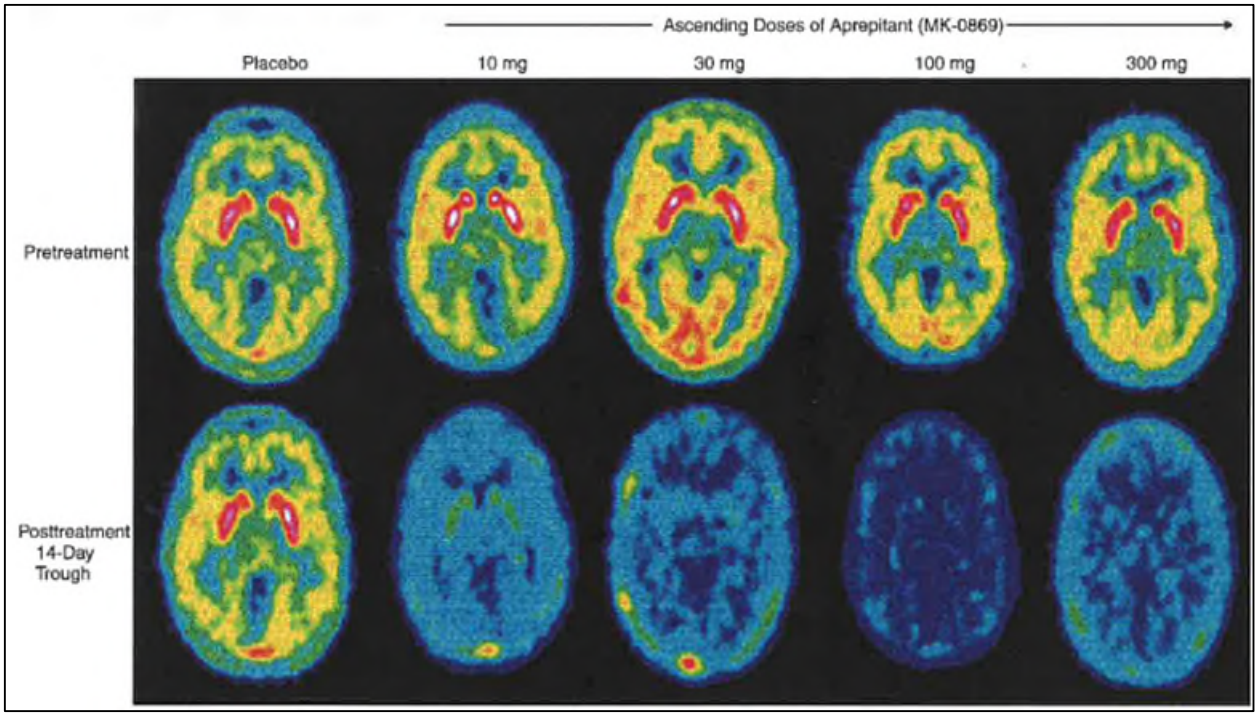
615. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).

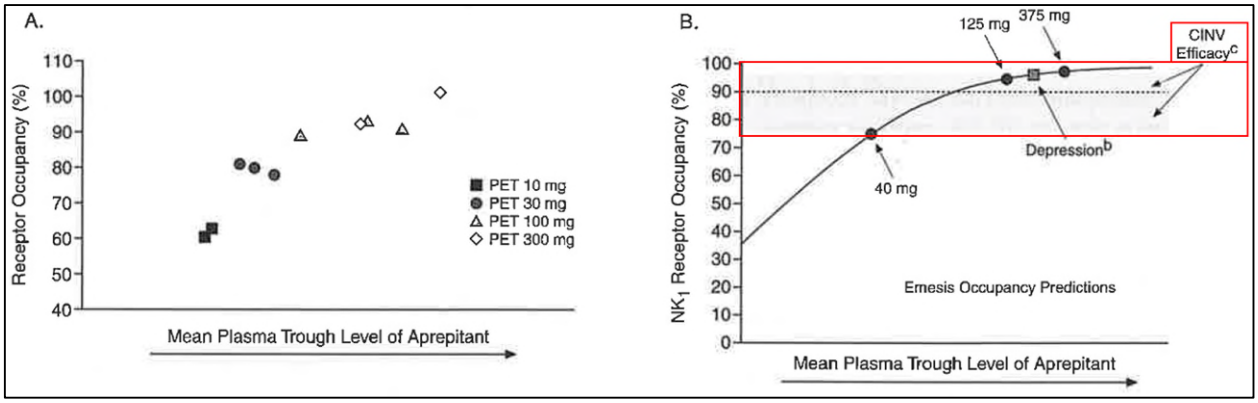


616. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS

(Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

617. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable

distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Sections V.C, V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See*, *e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Sections V.C, V.D, above. The '515 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration." EX1003 ('515 patent), 4:55-5:3. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

618. Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 1(b).

> **1(c).** wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if [sic] effective to treat said nausea and vomiting for said five consecutive days.

619. I have reproduced above the single dose (c) element of claim 1. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the single dose of claim 1(c).

620. Herrstedt discloses a single dose of NK_1 receptor antagonist is administered on day one of said five consecutive days. Herrstedt explains its aprepitant NK_1 receptor antagonist is administered on days one, two, and three:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3….

EX1010 (Herrstedt), 146. Herrstedt explains that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that a single dose of its NK_1 receptor antagonist is administered on day one. Poli-Bigelli confirms the dosing combination included a single dose of aprepitant on day one of the five consecutive day study. EX1039 (Poli-Bigelli), 3091 ("The aprepitant regimen consisted of ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral

dexamethasone 12 mg ***on Day 1***….”); *id.*, Abstract (evaluating results “during the 5-day period post-cisplatin”; evaluation of patients “[d]uring the 5 days after chemotherapy”). Hesketh likewise confirms the dosing combination included a single dose of aprepitant on day one of the five consecutive day study. EX1037 (Hesketh), 4113 (“Patients in the aprepitant group received ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg ***on day 1***….”); *id.*, Abstract (evaluation of patient response “on days 1 to 5” after chemotherapy). A POSA would have known orally administered aprepitant was available in capsules of either 40 mg, 80 mg, or 125 mg; thus the orally administered 125 mg dose of aprepitant administered on day one in Poli-Bigelli, Hesketh, and thus as summarized in Herrstedt, was a single dose of the NK_1 receptor antagonist. EX1030 (Emend label), 1; EX1031 (Archived Emend label), 1.

621. The combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of said five consecutive days, no further netupitant is administered during said five consecutive days, and the single dose of netupitant is effective to treat said nausea and vomiting for said five consecutive days. Herrstedt describes administering aprepitant on days one, two, and three of the five consecutive days. EX1010 (Herrstedt), 146. But as I explained above (Claim element 1(a)), the POSA had good reason to substitute Bös’ netupitant for Herrstedt’s aprepitant. Netupitant was known to have a large half-life value, thus

reducing any need for subsequent administrations of NK_1 receptor antagonist. EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). The POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination provided further reason to omit subsequent doses of NK_1 receptor antagonist because a single dose would sustain therapeutic efficacy. In other words, the POSA would have understood a single day one dose of netupitant to be effective to treat nausea and vomiting for the five consecutive days. Thus, the combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of said five consecutive days, no further netupitant is administered during said five consecutive days, and said single dose of netupitant is effective to treat said nausea and vomiting for said five consecutive days.

622. Herrington confirms a single dose of NK_1 receptor antagonist administered on day one of said five consecutive days, where no further NK_1 receptor antagonist is administered during said five consecutive days, is effective to treat nausea and vomiting for the five consecutive days. Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. Herrington describes that:

> The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy….

> From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

EX1016 (Herrington), Background. A POSA thus would have understood that the single administration of an NK_1 receptor antagonist on day one was similarly effective to the dosing protocol of Herrstedt dosing the NK_1 receptor antagonist on multiple days. Herrington reports this efficacy (to treat said nausea and vomiting) was evaluated across the entire five day period. EX1016 (Herrington), 2081 ("The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy."). Herrington reports the single day one dose of NK_1 receptor antagonist is effective to treat said nausea and vomiting for said five consecutive days:

> There were no significant differences between Arms A [3-day aprepitant] and B [single day one dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In ***Arms*** A and ***B, 93% of patients were emesis-free from Days 1-5*** compared with only 50% in Arm C [control group].

EX1016 (Herrington), Abstract. Herrington describes that the single day one dose of NK_1 receptor antagonist provided control against nausea across the five day period. *Id.*, 2086 ("The control of nausea was achieved in similar fashion between the 2 aprepitant arms."). Although Herrington identified "a trend toward better

significant nausea on Days 4-5 with the 3-day Arm A versus the single dose" the mean severity of nausea for the single dose of aprepitant was lower than the control test group across all five days. *Id.*, 2086, 2084 & Table 4 (reproduced below).

TABLE 4
Severity of Nausea Using VAS

	Severity of nausea using VAS (mean±SD; median, range)			
	Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	*P**	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0–95)	8.7 ± 15.7 0(0–60)	.82	15.6 ± 32.1 0(0–95)
Day 2	15.2 ± 24.6 4(0–95)	11.0 ± 16.1 1(0–50)	.80	28.4 ± 39.2 2.5(0–100)
Day 3	15.0 ± 26.1 1.5(0–95)	12.3 ± 16.5 2.5(0–50)	.95	30.3 ± 40.4 2.5(0–100)
Day 4	10.5 ± 21.8 3.5(0–95)	16.6 ± 23.6 2.5(0–75)	.62	19.6 ± 31.5 2.5(0–95)
Day 5	12.0 ± 25.2 0(0–95)	18.3 ± 27.2 0(0–80)	.52	20.6 ± 34.0 0(0–95)

VAS indicates visual analog scale; SD, standard deviation.
* Wilcoxon 2-sample test, (3-Day vs 1-Day).

Thus, Herrington confirms its single dose of aprepitant administered on day one, where no further NK_1 receptor antagonist is administered during the five day period, is effective to treat nausea and vomiting for the five consecutive days.

623. A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt's triple therapeutic combination for decreased costs, increased convenience, and patient preference for single

administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would have had good reason to employ the single dose of NK_1 receptor antagonist in the dosing protocol of Herrstedt without dosing on subsequent days. As discussed above, the POSA would have employed Bös' second generation NK_1 receptor antagonist—netupitant—in Herrstedt's protocol.

624. Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 1(c).

625. The combination of Herrstedt, Bös, Hargreaves, and optionally Herrington thus teaches all of the elements of claim 1 and rendered the claim obvious as a whole.

B. Claim 2

> **2.** The method of claim 1, wherein said netupitant occupies 80% or more of NK_1 receptors in the striatum seventy-two hours after said administration.

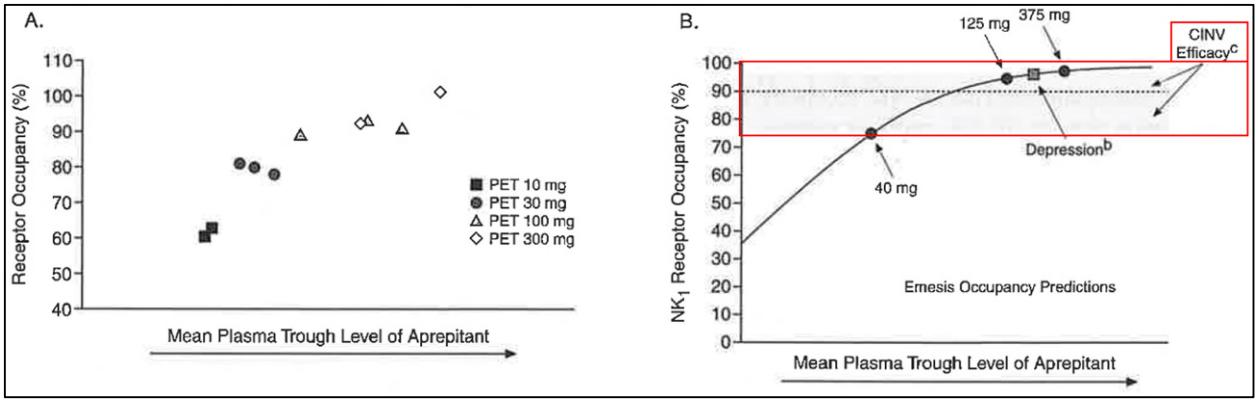
626. Claim 2 depends from independent claim 1 and additionally recites netupitant occupies 80% or more of NK_1 receptors in the striatum seventy-two hours after administration.

627. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

628. Hargreaves discloses that there is a direct relationship between occupancy of NK_1 receptors in the striatum and antiemetic effects for patients suffering from chemotherapy-induced nausea and vomiting, and that clinically effective doses of NK_1 receptor antagonists occupy at least 75-80% of NK receptors in the striatum of patients. Hargreaves discloses:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas ***the occupancy of ≥ 90% of NK_1 receptors*** requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of ***emesis blocked ≥ 90% of NK_1 receptors*** in the CNS (Figure 6B), whereas ***the*** initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B).

EX1012 (Hargreaves), 23. Thus, Hargreaves teaches the benefits of the NK_1 receptor antagonist occupying high levels of NK receptors in the striatum (e.g., greater than 90%). Reproduced below is an annotated version of Hargreaves Fig. 6.



Notably, Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy is present in a grayed-out region beginning at approximately 75% of NK_1 receptor occupancy. Thus, Hargreaves explicitly describes that a therapeutically effective amount of an NK_1 receptor antagonist is one which occupies high levels of NK_1 receptors (e.g., greater than 75% and preferably greater than 90%) in the striatum.

629. As described above (Section XIX.A), it would have been obvious in view of Hargreaves that a therapeutically effective dose of prophylactically administered netupitant occupies at least 70% of NK_1 receptors in the striatum after administration. As I describe herein, a skilled artisan would have found it obvious to administer 300 mg of netupitant as the therapeutically effective dose (Section XIX.J), and because of netupitant's long half-life, it is a natural result that the prophylactic administration of said therapeutically effective dose maintains at least 70% NK_1 receptor occupancy at 72 hours. The "at least 80%" occupancy limitation is substantially similar to the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount

of NK_1 receptor antagonist for the treatment of emesis. EX1012 (Hargreaves), 23 & Fig. 6. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the ’515 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the “at least 80%” occupancy limitation. For example, the examiner stated that netupitant occupying at least 80% of a patient’s striatum NK_1 receptors was an inherent feature of a therapeutically effective dose of netupitant. The examiner also stated that netupitant occupying at least 70% of a patient’s striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant during prosecution of the application that issued as the ’297 patent. EX1008, 120; Section V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner’s position. EX1008, 155; Section V.D, above. The ’515 patent specification reports this is a characteristic of netupitant itself: “netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration.”

EX1003 (’515 patent), 4:62-65. The patentee’s admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

630. Based on Hargreaves’ prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 90% (at least 80%) of NK_1 receptors in the striatum seventy-two hours after administration would be very likely to be efficacious for treating CINV.

631. Accordingly, it is my opinion that claim 2 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

C. Claim 3

> **3.** The method of claim 1, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

632. Claim 3 depends from independent claim 1 and additionally recites that the method further comprises a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when

administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose (i.e., having a different strength from day one) of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

633. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

> **3(a)[1].** The method of claim 1, further comprising: a) administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant,

634. I have reproduced above the administering step (a)[1] element of claim 3. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the administering step of claim 3(a)[1].

635. Before looking to evaluate whether the prior art discloses this limitation, I look to the specification of the ’515 patent exclusively to understand

what the claim means when it says a first dose of dexamethasone is "ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant." For example, the specification admits that a 20 mg dose of dexamethasone was known in the field as the minimum day-one therapeutically effective dose for treating CINV:

> The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be ***20 mg***. administered orally or by injection on day one, and sixteen mg. administered orally or by injection on days two, three and four. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the ***minimum effective dose of dexamethasone*** is ***20 mg***. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1003 ('515 patent), 8:20-30 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). As defined in the patent specification, the claim term "dose of dexamethasone which is ineffective against nausea and vomiting when administered alone" encompasses any day one dose of less than 20 mg. The prior art routinely described this same 20 mg dose as the standard day one dose for treating emetogenic chemotherapy. *See, e.g.*, EX1010 (Herrstedt), 145 ("single intravenous dose of 20 mg" for highly emetogenic chemotherapy); *see*

also, e.g., EX1025 (Chawla), 2292 (standard therapy combination included oral dexamethasone 20 mg on Day 1); EX1013 (MASCC), Table 3 (20 mg dexamethasone for patients not receiving aprepitant).

636. Understanding the claim term as illustrated in the patent specification, Herrstedt discloses administering to said patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with the NK_1 receptor antagonist. For example, Herrstedt teaches administering a single, sub-20 mg day one dose of dexamethasone for the treatment of moderately emetogenic chemotherapy, a treatment that leads to nausea and vomiting (e.g., CINV). EX1010 (Herrstedt), 145-147. In contrast to the standard 20 mg day one dose, Herrstedt teaches that the day one dexamethasone should be administered in a reduced amount—about 25% to 50% less than the 20 mg (minimally effective) standard dose discussed above. *Id.* Such reduced amount was, by itself, ineffective against the chemotherapy-induced nausea and vomiting, but when administered with the combination of therapeutics (including the NK_1 receptor antagonist), the reduced amount of dexamethasone was effective against nausea and vomiting.

637. Herrstedt explains that due to metabolic interactions of corticosteroids (e.g., dexamethasone or methylprednisolone) and the NK_1 receptor antagonist

(aprepitant), the corticosteroid should be administered in a lower-than-typically-therapeutic dose when treatment includes the NK_1 receptor antagonist. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

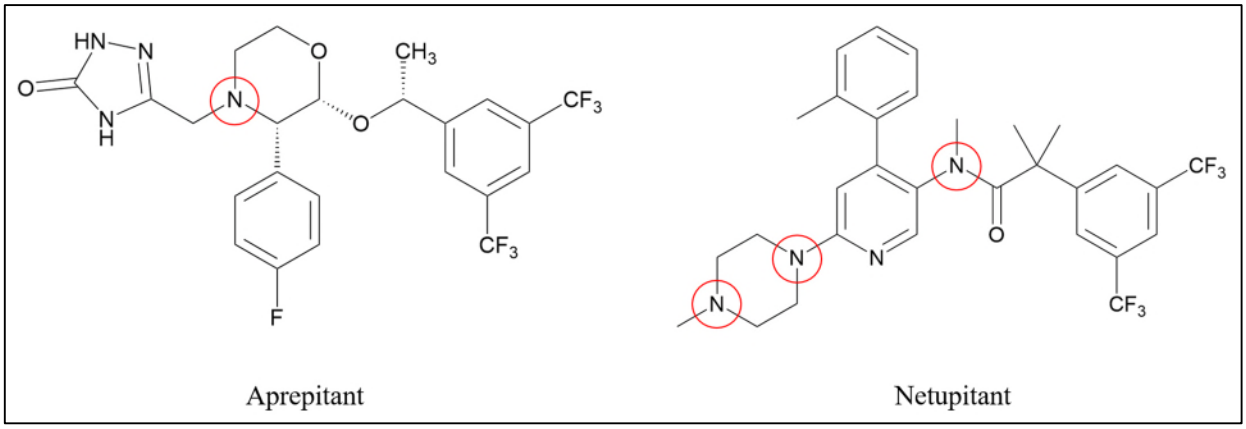
> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Therefore Herrstedt suggests the dose of dexamethasone—when administered with NK_1 receptor antagonist—should be a reduced dose which, by itself would be ineffective against nausea and vomiting, but when administered in combination with NK_1 receptor antagonist is effective against nausea and vomiting because it provides the same total exposure of dexamethasone AUC. Thus, Herrstedt describes administering to the patient on day one a first dose of dexamethasone which is ineffective against nausea and vomiting (e.g., CINV)

when administered alone, but effective against nausea and vomiting when administered in combination with the NK_1 receptor antagonist.

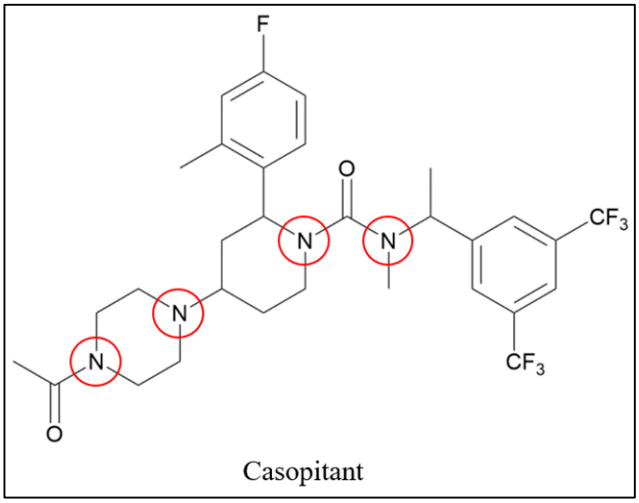
638. Based on the experience with aprepitant, a POSA would have had good reason to determine the dexamethasone AUC when administered with Bös' netupitant compared to administration of dexamethasone alone. Evaluating such drug-drug interactions was well-known and routine in the field. EX1049 (Zhou), 318 ("Drug-drug interactions remain an important issue in clinical practice and drug development"). Evaluating such drug-drug interactions (e.g., NK_1-receptor-antagonist-induced dexamethasone potentiation) was a fundamental prerequisite when administering a combination therapy, such as the combination antiemetic therapy at issue. EX1010 (Herrstedt), 147 ("Risk of drug-drug interactions with the use of anti-emetics" due to "concomitant treatment with supportive care drugs" should be evaluated). Understanding the interaction of therapeutic agents with their metabolism provided necessary insight for evaluating drug-drug interactions. EX1044 (Schoenwald), 86 ("By understanding which metabolic steps may be susceptible to induction or inhibition by other drugs, specific *in vitro* or clinical drug interaction studies may be conducted to determine the potential risks of drug-drug interactions."). Among other interactions, a POSA would have had good reason to measure the impact of netupitant administration on the cytochrome P450 (CYP) 3A4 ("CYP3A4") enzyme-mediated metabolism of dexamethasone. This

particular cytochrome P450 was known to "metaboliz[e] more than 50% of [] clinically used drugs." EX1049 (Zhou), 310. In addition to metabolizing "more than 50% [of] therapeutic drugs" CYP3A4 was known to have "very broad" substrate specificity "with an extremely large number of structurally divergent chemicals being metabolized." *Id.*, 311. In other words, it was well-known CYP3A4 had high "ligand promiscuity" for metabolism and a high likelihood of being involved in the metabolism of a given therapeutic agent. *Id.* Additionally, CYP3A4 was known to be inhibited by a variety of substrates sharing common structural features with aprepitant and netupitant. For example, drugs known to inactivate CYP3A4 "often possess a number of structural similarities such as a tertiary amine function[.]" EX1049 (Zhou), 314. Both aprepitant and netupitant had such tertiary amine function, as shown in the below figure (red circles annotating tertiary amines).



It was known that aprepitant was a substrate and moderate inhibitor of CYP3A4, leading to increased AUC exposure of dexamethasone. EX1010 (Herrstedt), 147

(50% increase of dexamethasone AUC). Likewise, it was known that the NK_1 receptor antagonist casopitant—structurally similar to netupitant—was also a substrate and weak-to-moderate inhibitor of CYP3A4, requiring "a reduction in dexamethasone dose of 40-50%, when repeat-dose oral dexamethasone is to be co-administered with oral casopitant." EX1042 (Ruhlmann), 377-378; *see also* the below figure where I provide the structure with annotations of tertiary amines.



Casopitant

Thus, a POSA would have expected netupitant to similarly act as substrate and inhibitor of CYP3A4. Accordingly, it would have been obvious and routine to a POSA in view of Herrstedt, Bös, Hargreaves, and optionally Herrington to measure the impact of netupitant co-administration on dexamethasone AUC and to lower the dexamethasone dose accordingly. Because the patent defines the sub-therapeutic dose of dexamethasone to encompass any day one dose below the standard 20 mg dose, any actual reduction from the standard day one dose satisfies the claims.

639. Having good reason to co-administer netupitant with dexamethasone (as discussed above), the reduced metabolism of dexamethasone when co-administered with netupitant is a property that necessarily and naturally flows from the combination. Accordingly, a POSA performing routine metabolism studies on the combination therapy would reasonably expect to measure the increased dexamethasone AUC and to reduce the dexamethasone dose below the 20 mg (minimally effective) standard dose, which dose reduction the patent itself admits satisfies the claim.

640. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 3(a)[1].

> **3(a)[2].** Wherein said first dose comprises from 50 to 70% of a minimum effective dose when administered alone; and

641. I have reproduced above the decreased dexamethasone dose (a)[2] element of claim 3. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the decreased dexamethasone dose of claim 3(a)[2].

642. As I explained above for element 3(a)[1], Herrstedt explains the day one dose of dexamethasone should be administered in a reduced amount—including by about 50 to 70%—compared to the 20 mg dose. As I explained above, it was known NK_1 receptor antagonists doubled the AUC concentration of

dexamethasone, and Herrstedt teaches reducing the dexamethasone dose in a corresponding amount. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Herrstedt thus teaches reducing the day one dose of oral dexamethasone, when administered with an NK_1 receptor antagonist, by about 50% of the minimum effective dose when administered alone to achieve the same effective AUC concentration. Accordingly, Herrstedt discloses element 3(a)[2]. *See also* Sections IX.A, IX.E, above (prior art taught to reduce dexamethasone when administered with NK_1 receptor antagonists).

643. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 3(a)[2].

> **3(b).** b) if said patient is subject to highly emetogenic chemotherapy, administering to said patient, on days two, three and four, a second dose of dexamethasone which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said netupitant, wherein said second dose comprises from 40 to 60% of a minimum effective dose when administered alone.

644. I have reproduced above the subsequent day administration (b) element of claim 3. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the decreased dexamethasone dose of claim 3(b).

645. Herrstedt describes its patients are subject to highly emetogenic chemotherapy and its method further comprises administering to said patients, on days two, three, and four, a second dose (i.e., having a different strength from day one) of dexamethasone. Herrstedt identifies several studies having such dosing:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, dexamethasone and aprepitant day 1 followed by ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection

days 2–4.

EX1010 (Herrstedt), 146; *id.* (studies involved "patients receiving ***cisplatin-based, highly emetogenic chemotherapy***"); *see also* Section VIII, above (routine protocol to dose dexamethasone on subsequent days).

646. Herrstedt suggests the days 2-4 doses of dexamethasone are ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with said NK_1 receptor antagonist. Herrstedt teaches that a lower dose of corticosteroids, such as dexamethasone, should be administered when concomitantly administered with an NK_1 receptor antagonist due to resulting increase of AUC exposure. EX1010 (Herrstedt), 147-148; *see also* Section IX.E, above. Thus, when the lower dose of dexamethasone is administered alone against HEC-induced nausea and vomiting (i.e., in absence of NK_1 receptor antagonist) it is ineffective against chemotherapy-induced nausea and vomiting, but when administered in combination with the NK_1 receptor antagonist, the lower dose is effective in increasing the efficacy of the combination treatment. *See also* above discussion (known CYP3A4 metabolism interaction and corresponding decrease of dose of dexamethasone).

647. Herrstedt also suggests said second dose comprises from 40 to 60% of a minimum effective dose when administered alone. EX1010 (Herrstedt), 146-147. Herrstedt teaches when corticosteroid (e.g., methylprednisolone) is orally

administered with NK_1 receptor antagonist (aprepitant), the dose should be reduced "by 50% to obtain the same exposure." EX1010 (Herrstedt), 147. This is an amount which is ineffective against nausea and vomiting when administered alone, but effective against nausea and vomiting when administered in combination with an NK_1 receptor antagonist. Herrstedt explains dexamethasone and methylprednisolone are both sensitive to CYP3A4 in the same manner, thus a 50% reduction should be applied to both. EX1010 (Herrstedt), 147. I explained above that NK_1 receptor antagonists doubled the AUC concentration of dexamethasone, thus it was obvious to correspondingly halve the dexamethasone dose. *See* Sections XV.A, IX.E, above; EX1010 (Herrstedt), 147. A POSA would have expected similar increase in dexamethasone AUC exposure following administration of netupitant. Furthermore, Herrstedt discloses that administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study," each of which discloses the subsequent doses of dexamethasone comprise 8 mg (50% of the 16 mg minimum effective dose (EX1001 ('515 patent), 8:20-30 ("The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, ***has been demonstrated to be***…***sixteen mg.*** administered orally or by injection ***on days two, three and four***") (citing EX1019 (Jordan)))), confirming that Herrstedt teaches reducing the day one dose. EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)); EX1039 (Poli-

Bigelli), Abstract ("oral dexamethasone ***8 mg once daily on Days 2-3***; and oral dexamethasone ***8 mg on Day 4***"); EX1037 (Hesketh), 4113 (similar). Herrstedt also teaches an effective amount of NK_1 receptor antagonist is present in the patient in subsequent days. For example, when aprepitant is used as the NK_1 receptor antagonist, it is dosed on days 2-3 (EX1010 (Herrstedt), 146), and it was known netupitant had increased receptor affinity and increased half-life (EX1014 (Bös), 19:3-10 (24-30 hours)).

648. The POSA would have good reason to administer doses of dexamethasone on days two, three, and four in a reduced amount to account for increased AUC exposure based on the continued presence of the NK_1 receptor antagonist. Because NK_1 receptor antagonist doubled dexamethasone AUC, a POSA would have reduced the dexamethasone dose by about 50% to obtain the same total AUC concentration. This reduced amount (50% of the minimally effective dose) of dexamethasone would have been ineffective for antiemetic effect when administered as a monotherapy, but would be expected to be effective when combined with NK_1 receptor antagonists due to the increased AUC concentration. *See also* Section IX.E, above (known to administer dexamethasone in a reduced dose on days subsequent to chemotherapy treatment when therapy included an NK_1 receptor antagonist).

649. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 3(b).

650. Thus, it is my opinion that claim 3 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

D. Claim 4

> **4.** The method of claim 1 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and b) administering about 12 mg. of dexamethasone on day one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

651. Claim 4 depends from independent claim 1 and additionally recites: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg of netupitant as the free base; and b) administering about 12 mg of dexamethasone on day one; and c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg of dexamethasone on days two, three and four.

652. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

> **4(a).** The method of claim 1 wherein: a) only one dose of netupitant is administered during said five days on day one, comprising about 300 mg. of netupitant as the free base; and

653. I have reproduced above the netupitant dose (a) element of claim 4. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the netupitant dose of claim 4(a).

654. I explained above (Claim 1) that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests administering only one dose of netupitant during said five days on day one. *See* Section XIX.A, above. Briefly, Herrstedt discloses a single dose of NK_1 receptor antagonist is administered on day one of said five consecutive days. EX1010 (Herrstedt), 146; *see also* EX1039 (Poli-Bigelli), 3091 ("The aprepitant regimen consisted of ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg ***on Day 1***…."); *id.*, Abstract (evaluating results "during the 5-day period post-cisplatin"; evaluation of patients "[d]uring the 5 days after chemotherapy"); EX1037 (Hesketh), 4113 ("Patients in the aprepitant group received ***oral aprepitant 125 mg*** plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg ***on day 1***…."); *id.*, Abstract (evaluation of patient response "on days 1 to 5" after chemotherapy). A POSA would have known the 125 mg orally administered aprepitant was a single dose. EX1030 (Emend label), 1; EX1031 (Archived Emend label), 1. While Herrstedt describes administering aprepitant on days one, two, and three of the five consecutive days, the POSA had good reason to substitute Bös' netupitant for Herrstedt's aprepitant. Netupitant was known to have a large half-

life value, thus reducing any need for subsequent administrations of NK_1 receptor antagonist. EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). The POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination provided further reason to omit subsequent doses of NK_1 receptor antagonist because a single dose would sustain therapeutic efficacy. In other words, the POSA would have recognized good reason to administer only one dose of netupitant during said five days on day one.

655. Herrington confirms only one dose of NK_1 receptor antagonist is administered during said five days on day one. Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. EX1016 (Herrington), Background. Herrington reports a single dose of NK_1 receptor antagonist effectively treated nausea and vomiting, as evaluated across the entire five day period. EX1016 (Herrington), 2081, Abstract. Herrington also describes that its single day one dose of NK_1 receptor antagonist provided control against nausea across the five day period. *Id.*, 2086 & Table 4. Thus, Herrington confirms only one dose of NK_1 receptor antagonist is administered during the five days on day one, and such administration is effective to treat nausea and vomiting.

656. Bös teaches the dose of netupitant comprises about 300 mg as the free base. Bös discloses a therapeutically effective amount of NK_1 receptor antagonists

(including netupitant) comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

657. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, Hargreaves, and optionally Herrington to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000

mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating nausea and vomiting.

658. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '515 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '515 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1003 ('515 patent), 8:13-19. Therefore, the '515 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg dose of netupitant. Thus, it is my opinion that the POSA would have

had good reason to select a dose of about 300 mg when determining the amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

659. The ’515 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’515 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1003 (’515 patent), 16:34-17:2) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1003 (’515 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 17:4-29), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’515 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

660. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 4(a).

4(b). b) administering about 12 mg. of dexamethasone on day one; and

661. I have reproduced above the day one dexamethasone dose (b) element of claim 4. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the day one dexamethasone dose of claim 4(b).

662. Herrstedt discloses administering dexamethasone in conjunction with administering the NK_1 receptor antagonist. As discussed above, Herrstedt provides a summary of two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, Section XIX.A. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that in Herrstedt, 12 mg of dexamethasone was administered on day one. Poli-Bigelli and Hesketh both expressly confirm 12 mg of dexamethasone was administered on day one. Poli-Bigelli administers, for the regimen using NK_1 receptor antagonist, "oral dexamethasone 12 mg on Day 1." EX1039 (Poli-Bigelli), 3091. Likewise, Hesketh administers, for its regimen using NK_1 receptor antagonist, "oral dexamethasone 12 mg on day 1." EX1037 (Hesketh), 4113. Thus,

a POSA would have had good reason to administer about 12 mg of dexamethasone on day one, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

663. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 4(b).

> **4(c).** c) if said patient is undergoing highly emetogenic chemotherapy, administering about 8 mg. of dexamethasone on days two, three and four.

664. I have reproduced above the days 2-4 dexamethasone dose (c) element of claim 4. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests the days 2-4 dexamethasone dose of claim 4(c).

665. Herrstedt discloses, for patients undergoing highly emetogenic chemotherapy, administering dexamethasone in conjunction with administering the NK_1 receptor antagonist. Herrstedt summarizes two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, Section XIX.A. These studies investigated the use of an NK_1 receptor antagonist "in patients receiving ***cisplatin-based, highly emetogenic chemotherapy***." EX1010 (Herrstedt), 146. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA

reviewing Herrstedt would have understood that in Herrstedt, 8 mg dexamethasone was administered on days two, three and four for patients undergoing highly emetogenic chemotherapy. Poli-Bigelli and Hesketh both expressly confirm 8 mg dexamethasone was orally administered on days two, three and four. Poli-Bigelli administers, for the regimen using NK_1 receptor antagonist, "oral dexamethasone 8 mg once daily on Days 2 and 3; and oral dexamethasone 8 mg on Day 4." EX1039 (Poli-Bigelli), 3091. Likewise, Hesketh administers, for its regimen using NK_1 receptor antagonist, "oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4." EX1037 (Hesketh), 4113. Each study concerned the antiemetic effect of the therapy for patients receiving the highly emetogenic chemotherapy, cisplatin. EX1039 (Poli-Bigelli), Abstract; EX1037 (Hesketh), Abstract. Thus, a POSA would have had good reason to orally administer about 8 mg of dexamethasone on days two, three and four, to patients undergoing highly emetogenic chemotherapy and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

666. Accordingly, it is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses the subject matter recited in claim element 4(c).

667. Thus, it is my opinion that claim 4 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

E. Claim 5

> **5.** The method of claim 1 wherein said nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"), radiation therapy induced nausea and vomiting ("RINV"), or post-operative nausea and vomiting ("PONV").

668. Claim 5 depends from independent claim 1 and additionally recites the nausea and vomiting is chemotherapy induced nausea and vomiting, radiation therapy induced nausea and vomiting, ***or*** post-operative nausea and vomiting.

669. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

670. Herrstedt explains the nausea and vomiting is chemotherapy induced nausea and vomiting ("CINV"). Herrstedt describes its combination therapy is used as a prophylactic to treat nausea and vomiting that is chemotherapy induced nausea and vomiting (CINV). Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as '***no emesis and no rescue therapy*** on days 1–5 postcisplatin', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt's disclosure is generally directed to "treatment of nausea and vomiting from chemotherapy." *Id.*, Abstract. A POSA therefore would have understood Herrstedt's administration of prophylactic is a method for

treating both nausea and vomiting (*see* Claim 1) and that the nausea and vomiting is chemotherapy-induced nausea and vomiting (CINV).

671. Accordingly, it is my opinion that claim 5 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

F. Claim 6

> **6.** The method of claim 1 wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

672. Claim 6 depends from independent claim 1 and additionally recites that the nausea and vomiting is induced by moderately or highly emetogenic chemotherapy.

673. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

674. Herrstedt discloses wherein said nausea and vomiting is induced by moderately or highly emetogenic chemotherapy. As detailed above, Herrstedt discloses its antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy. *See* Claim 5, above. Herrstedt also describes efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***." EX1010 (Herrstedt), Abstract. Herrstedt explains:

Four phase III trials have investigated the use of aprepitant in patients

> receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of ***cyclophosphamide plus an anthracycline***. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt also includes a table of chemotherapies and classifies cisplatin as highly emetogenic. *Id.*, Table 1. Another of Herrstedt's tables categorizes the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic. *Id.*, Table 4. Thus, the studies described above in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by moderately or highly emetogenic chemotherapy. EX1010 (Herrstedt), 146.

675. Accordingly, it is my opinion that claim 6 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

G. Claim 7

> **7.** The method of claim 1 comprising administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

676. Claim 7 depends from independent claim 1 and additionally recites that the method comprises administering moderately or highly emetogenic chemotherapy within from about one hour to about two hours of said administration of said netupitant or pharmaceutically acceptable salt thereof.

677. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

678. Herrstedt discloses administering moderately or highly emetogenic chemotherapy in conjunction with administering the NK_1 receptor antagonist. Herrstedt provides a summary of two studies employing the triple anti-emetic drug combination described above. *See* Claim 1, above. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) was obvious. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

679. A POSA reviewing Herrstedt would have understood that the chemotherapy in Herrstedt was administered within from about one hour to about two hours of the NK_1 receptor antagonist, consistent with routine practice. *See, e.g.*, EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist aprepitant administered one hour prior to cisplatin); EX1037 (Hesketh), 4113 (same); EX1014 (Bös), 19:15-20 (NK_1 receptor antagonist netupitant administered up to two hours before emetogen). Poli-Bigelli and Hesketh both expressly confirm that the highly emetogenic chemotherapy (cisplatin) was administered one hour after the

administration of the NK_1 receptor antagonist (aprepitant). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin, patients received either aprepitant or placebo***. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing aprepitant one hour prior to administration of cisplatin (and in combination with the other drugs disclosed in the regimen) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin, patients received either aprepitant or placebo***. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer moderately or highly emetogenic chemotherapy within from about one hour to about two hours of the administration of netupitant or pharmaceutically acceptable salt thereof, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

680. Accordingly, it is my opinion that claim 7 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

H. Claim 8

> **8.** The method of claim 1 comprising treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

681. Claim 8 depends from independent claim 1 and additionally recites that the method comprises treating nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase, or in response to highly emetogenic chemotherapy during the delayed phase, or in response to moderately emetogenic chemotherapy during the acute phase, or in response to moderately emetogenic chemotherapy during the delayed phase.

682. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

683. Herrstedt discloses treating nausea and vomiting in response to highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"). Herrstedt discloses its NK_1 antiemetic combination provides therapeutic effect for "emesis induced by highly or moderately emetogenic chemotherapy" noting in particular that the NK_1 receptor antagonist is

"also active in the protection against delayed emesis." *Id.*, Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

684. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was used to treat nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and in response to highly emetogenic chemotherapy during the delayed phase. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing combination treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.
*$P < .05$ versus standard therapy (significance based on logistic regression model).
†$P < .01$ versus standard therapy (significance based on logistic regression model).
‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.
§Analysis not planned.

Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, and would have had a reasonable expectation of success that such dosing would treat nausea and vomiting in response to highly emetogenic chemotherapy during the acute phase and also would treat nausea and vomiting in response to highly emetogenic chemotherapy during the delayed phase.

685. Accordingly, it is my opinion that claim 8 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

I. Claim 9

> **9.** The method of claim 1, comprising administering from about 200 to about 400 mg of netupitant as the free base.

686. Claim 9 depends from independent claim 1 and additionally recites administering from about 200 to about 400 mg of netupitant as the free base.

687. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

688. Bös teaches administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—in a range that includes from about 200 mg to about 400 mg as the free base. Bös discloses a family of NK_1 receptor antagonists including netupitant are useful for treating chemotherapy-induced emesis. EX1014 (Bös), 2:1-65, 14:9-20. Bös discloses an administration dose

range for its NK_1 receptor antagonists (including netupitant) that encompasses the claimed range from about 200 to about 400 mg. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

689. Bös explicitly recognizes the application of its NK_1 receptor antagonists "for treatment induced vomiting" including "the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist." *Id.*, 1:60-64. Bös describes netupitant and its synthesis (*id.*, 14:9-15:20 (Formula Ib is netupitant)) and explains that netupitant "is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)" (*id.*, 14:32-38). *See also id.*, 18:42-19:38 (favorable in vitro and in vivo studies as well as oral bioavailability and half-life results).

690. It is my opinion that a POSA would have recognized Bös' range spanning two orders of magnitude (about 10 to 1,000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts. It is my opinion that the POSA would have had good reason to optimize Bös' range when determining the

therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22; Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect administering that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

691. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '515 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '515 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1003 ('515 patent), 8:13-19. Therefore, the '515 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at

the 200-400 mg therapeutic dose range of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a range including from about 200 to about 400 mg when determining the amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

692. Accordingly, it is my opinion that claim 9 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

J. Claim 10

> **9.** The method of claim 1, comprising orally administering about 300 mg of netupitant as the free base.

693. Claim 10 depends from independent claim 1 and additionally recites orally administering about 300 mg of netupitant as the free base.

694. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington. *See* Section XIX.A, above.

695. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

696. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, Hargreaves, and optionally Herrington to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA would have had a reasonable expectation of identifying through such a routine

dose-ranging study a therapeutically effective amount of netupitant for treating nausea and vomiting.

697. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the ’515 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the ’515 patent specification, which explains:

> As used herein, “therapeutically effective amount” refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1003 (’515 patent), 8:13-19. Therefore, the ’515 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to orally administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

698. The ’515 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’515 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1003 (’515 patent), 16:34-17:2) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1003 (’515 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 17:4-29), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’515 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

699. Accordingly, it is my opinion that claim 10 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

K. Claim 18

18. The method of claim 17, wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration.

700. Claim 18 depends from dependent claim 17 and additionally recites said netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration.

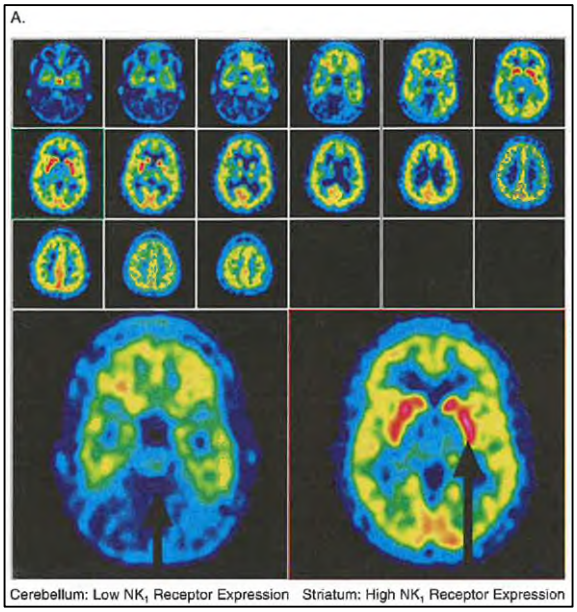
701. As I previously addressed above, claim 17 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XVIII.G, above. A POSA would have had good reason to evaluate NK_1 receptor occupancy using Hargreaves' PET imaging with a reasonable expectation of success for at least the same reasons provided above in Claim 1. *See* Section XIX.A.

702. It is my opinion that the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration as recited in claim 18.

703. Hargreaves explains that for NK_1 receptor antagonists to be therapeutically effective, they must interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as

striatum…."), Fig. 4. Bös describes netupitant has high affinity for the NK_1 receptor antagonist (EX1014 (Bös), 18:42-48) and belongs to a family of compounds that are therapeutically effective when administered. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"); *id.*, 18:64-19:30 (in vivo testing confirming efficacy). Hargreaves' data demonstrate that aprepitant passes into the CNS and binds to NK_1 receptors, including in the striatum.

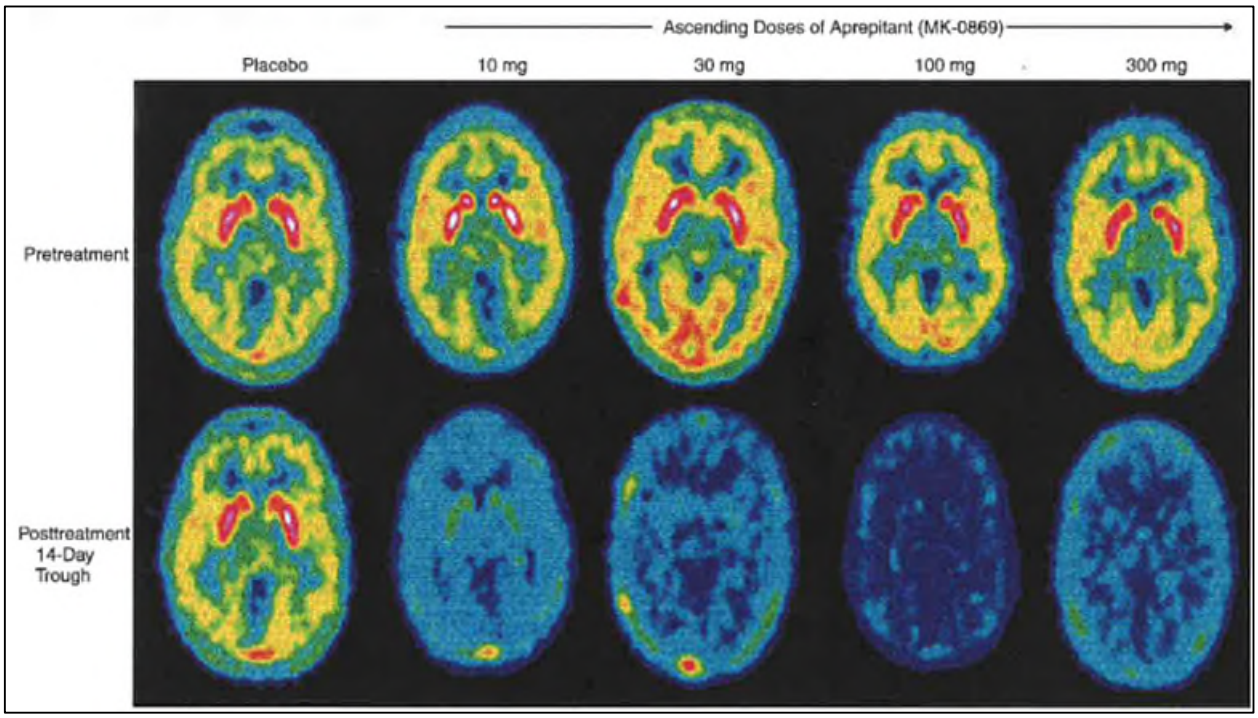
704. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

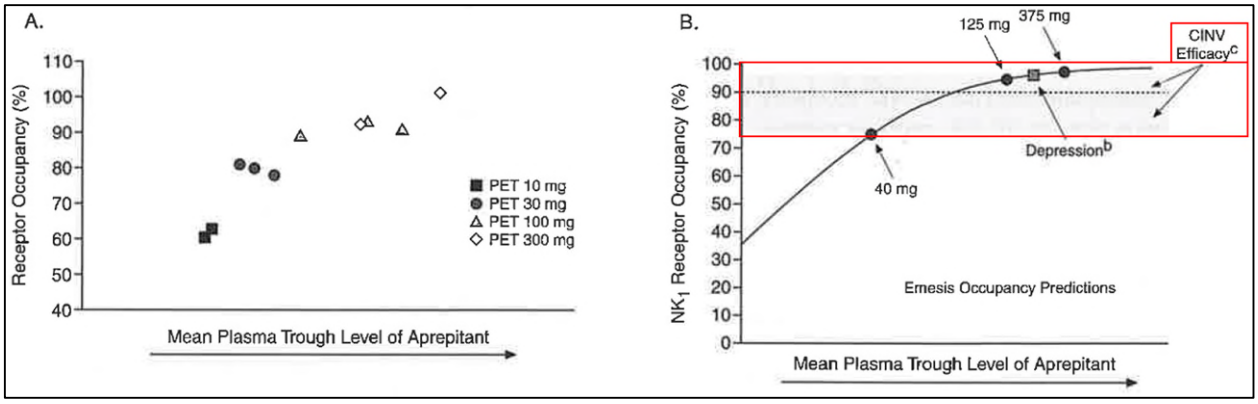
EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).



705. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS (Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests netupitant occupies at least 70% of said patient's striatum NK1 receptors after administration as recited in claim 18. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum ninety-six hours after administration would be very likely to be efficacious for treating CINV.

706. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's

striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Sections V.C-V.D, above. Furthermore, seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days (and 4 days) into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Sections V.C-V.D, above. The '515 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors ***even ninety-six hours*** after administration." EX1003 ('515 patent), 4:55-5:3. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

707. Accordingly, it is my opinion that claim 18 as a whole was also obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

L. Motivation to Combine

708. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to moderately or highly emetogenic chemotherapy with the antiemetic combination therapy

provided in Herrstedt, using therapeutically effective amounts of the second generation NK_1 receptor antagonist as claimed. *See* Section XIX.A, above. I described that persons having ordinary skill in the art would have had good reason to prophylactically treat (on Day 1, prior to chemotherapy) patients receiving emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt antiemetic therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (NK_1 receptor antagonist administered with dexamethasone on Day 1 provided antiemetic effect).

709. The person having ordinary skill in the art also would have modified the Herrstedt antiemetic therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37; Section XIX.A, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*,

19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös explained the netupitant is administered orally (administration of oral doses as compared to intravenous has benefits as I described above) (*id.*, 19:2-38) and provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

710. To evaluate the amount necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

711. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt antiemetic combination therapy with Bös'

second generation NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving emetogenic chemotherapy during the acute and delayed phases.

712. The skilled artisan also would have had good reason to modify the Herrstedt antiemetic therapy to administer Bös' NK_1 receptor antagonist (netupitant) on a single day (day one). Herrington explains there was no observed benefit in administering aprepitant on multiple consecutive days (i.e., days 1-3 of a chemotherapy treatment) as compared to administration of a single dose on only day one. EX1016 (Herrington), Abstract, 2083-2084. The person having ordinary skill in the art would have understood that decreasing the number of administrations of a therapeutic increases was preferred by patients and provides additional ease of administration. *See* Section IX.G. The POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen…."). Thus, the POSA would have had good reason to modify the Herrstedt protocol to use the Herrington oral administration of NK_1 receptor antagonist on a single day (i.e., day one).

M. Reasonable Expectation of Success

713. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt antiemetic combination therapy with the claimed netupitant. A person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve a similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant.

714. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XIX.A, above.

715. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and Hargreaves to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention. A POSA would have had a reasonable expectation of success in achieving a therapeutically effective result by modifying Herrstedt to administer the NK_1 receptor antagonist netupitant orally on a single day (prophylactically, day one of a chemotherapy treatment). Herrington explains the single dose of NK_1 receptor antagonist aprepitant was just as effective as multiple doses of the aprepitant, yielding similar overall therapeutic effect including anti-nausea treatment. EX1016 (Herrington), 2083-2084. Because Herrington shows similar results with a single dose of aprepitant, the POSA would have had a reasonable expectation of success in providing similar therapeutic effect with the single netupitant dose. Additionally, the POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen…."). A

POSA would have had a reasonable expectation that netupitant would perform in the same manner because it was known that netupitant acted through the same mechanism to provide the same therapeutic effect and because netupitant was known to have a longer half-life. *See, e.g.*, EX1014 (Bös), 19:3-38. Such properties could further be readily confirmed via the PET studies described by Hargreaves.

716. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Hargreaves, and optionally Herrington to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XX. [’297 PATENT GROUND 1] ’297 PATENT CLAIMS 1-4, 8-13, 17-19, AND 23 WERE OBVIOUS OVER HERRSTEDT AND BÖS

717. For the reasons discussed in detail below, it is my opinion that each of claims 1-4, 8-13, 17-19, and 23 of the ’297 patent was obvious as a whole. The obviousness of claims 1-4, 8-13, 17-19, and 23 is exemplified by disclosures in the Herrstedt and Bös.

718. I have evaluated below whether the combination of Herrstedt and Bös discloses each and every element of each of claims 1-4, 8-13, 17-19, and 23 of the ’297 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of

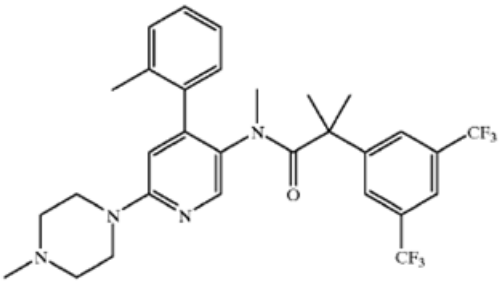
success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

719. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010 (Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt discloses administering to the patient on day one a therapeutically effective amount of a 5-HT_3 receptor antagonist (EX1010 (Herrstedt), 146) and teaches that palonosetron is a new 5-HT_3 receptor antagonist (*Id.*). Herrstedt also discloses administering to the patient on day one a first dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps in the dosing regimen are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146. Further, Herrstedt describes the above steps are effective for treating both nausea and vomiting to a greater extent during the 5-day period as compared to a

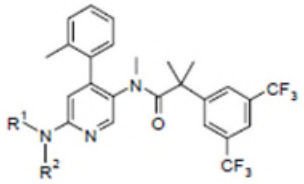
drug combination of just the 5-HT_3 receptor antagonist and dexamethasone. *Id.*, 146-147. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

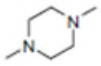
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*, 17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1

receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in Herrstedt.

720. The sections below explain in more detail how Herrstedt and Bös disclose each and every element of claims 1-4, 8-13, 17-19, and 23. I first analyze independent claims 1-3 of the challenged '297 patent. Thereafter, I analyze dependent claims 4, 8-13, 17-19, and 23.

A. Claim 1

> **1[pre].** A method of preventing acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising

721. I have reproduced above the preamble of claim 1 of the '297 patent. Herrstedt teaches a "method of preventing acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy" as disclosed in the preamble of claim 1. For example, Herrstedt teaches a method for preventing "[c]hemotherapy-induced ***nausea and vomiting***" in a subject with an antiemetic drug combination. EX1010 (Herrstedt), 143; *id.*, 144 ("Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy."), 146. Herrstedt discloses the triple-therapy combination of NK_1 receptor antagonist (aprepitant), 5-HT_3 receptor antagonist (ondansetron), and dexamethasone is an antiemetic useful for preventing chemotherapy-induced

nausea and vomiting. *Id.*, 146. Herrstedt describes administering its combination therapy to prevent nausea and vomiting "in patients ***receiving*** cisplatin-based, ***highly emetogenic chemotherapy***." *Id.*, 146.

722. Herrstedt discloses the antiemetic combination is effective to treat nausea and vomiting during the acute and delayed phases of emesis. Herrstedt's NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed*** emesis." EX1010 (Herrstedt), Abstract. Summarizing MASCC guidelines, Herrstedt identifies use of an NK_1 receptor antagonist (aprepitant) in combination with other agents as effective to treat nausea and vomiting during the acute and delayed phases. EX1010 (Herrstedt), 148-149 & Table 4 (reproduced below).

Table 4.

Summary of the recommendations in the MASCC guidelines [2].

Prophylaxis of acute nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Serotonin antagonist + dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Serotonin antagonist + dexamethasone + aprepitant
Moderate (other than AC)	Serotonin antagonist + dexamethasone
Low	Dexamethasone
Minimal	No routine prophylaxis
Prophylaxis of delayed nausea and vomiting	
Emesis risk group	Anti-emetics*
High	Dexamethasone + aprepitant
Anthracycline + cyclophosphamide (AC)	Aprepitant or dexamethasone
Moderate (other than AC)	Dexamethasone, a serotonin antagonist may be used as an alternative
Low	No routine prophylaxis
Minimal	No routine prophylaxis

*Recommended doses of anti-emetics are given in reference [48].

Herrstedt describes studies treating nausea and vomiting with a therapeutically effective amount of the NK_1 receptor antagonist and further discloses that the

administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

723. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt treated nausea and vomiting during the acute and delayed phases of emesis. For example, Herrstedt describes its combination therapy provided an improvement in the "complete response," which Herrstedt explains is the combination of both acute and delayed phases following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the dosing combination treats of nausea and vomiting in response to chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096.

724. Hesketh also confirms the dosing combination of Herrstedt treats nausea and vomiting in response to chemotherapy during ***both the acute phase and the delayed phase***. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

725. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 1.

> **1(a).** inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

726. I have reproduced above the inducing step (a) element of claim 1. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the inducing step of claim 1(a).

727. I explained at length above why administering therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone was obvious in view of the prior art discussed herein. As I explain below, palonosetron and netupitant are delivered to the relevant receptors (e.g., 5-HT_3 and NK_1 receptors in the CNS) through the circulatory system. Essentially, therapeutically effective levels of these antagonists are achieved in the blood, normally via intravenous or oral administration, causing therapeutically effective amounts of these antagonists to arrive at the target receptors in the CNS. In the normal course, administering therapeutically effective amounts of palonosetron and netupitant thus operates by "inducing in said subject therapeutically effective blood levels of palonosetron and netupitant." Accordingly, the prior art teaches, suggest, or renders obvious this element for the same reasons discussed above that it teaches, suggests, or renders obvious oral or intravenous administration of

therapeutically effective amounts of palonosetron and netupitant, in a combination regimen with dexamethasone.

728. Moreover, I observe that nowhere in the ’297 patent specification is there any discussion of “blood levels” let alone any definition of what constitutes “therapeutically effective blood levels.” The ’297 patent includes one example (Example 2) that measured pharmacokinetics of therapeutics using blood sampling but does not indicate what, if any, of the results disclose therapeutically effective blood levels. EX1004 (’297 patent), 14:50-67. Indeed, ’297 Example 2 is not concerned with therapeutic effectiveness but rather with confirming that “palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron.” *Id.*, 15:47-54.

729. The prosecution history suggests the claimed “therapeutically effective blood levels” is achieved by administering (orally or by i.v.) a therapeutically effective amount. During prosecution of the application that issued as the ’297 patent, I understand the examiner treated the recited blood level as equivalent to “effective amounts of each component to prevent acute and delayed emesis in patients receiving highly emetogenic cancer chemotherapy[.]” EX1008 (file history of ’050 application), 120; *see also id.*, 166-167. I also understand that the patent applicant did not rebut the examiner’s understanding, but instead argued

there was (i) unexpected results from the combination of palonosetron and netupitant; (ii) no reasonable likelihood of predicting the dose of netupitant; and (iii) no reasonable expectation netupitant would be independently effective. EX1008 (file history of ’050 application), 152-156. Thus, it is my understanding that the patent applicant agreed the claim term “therapeutically effective blood levels” of a drug is achieved by administering (orally or by i.v.) a “therapeutically effective amount” of said drug.

730. Related prosecution history confirms that the claimed “therapeutically effective blood levels” is achieved by administering (orally or by i.v.) a therapeutically effective amount of a drug. During prosecution of the application that issued as the ’357 patent, the patent applicant provided to the USPTO a table showing where the specification supported certain claim limitations. EX1006 (file history of ’927 application), 293-294. In that table, the applicant indicated that “netupitant blood levels effective to treat CINV during acute and delayed phase” and “palonosetron blood levels effective to treat CINV during acute phase” were solely supported by “Table 5” of the specification. *Id.*, 294. I reproduce below Table 5 from that specification:

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, -24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

EX1006 (file history of ’927 application), 127; *see also* EX1004 (’297 patent), Table 5 (same). This table does not disclose any measurement of blood levels and instead attributes efficacy to therapeutically effective doses of netupitant and palonosetron. Thus, patent applicant itself treated therapeutically effective blood levels of a drug as achieved by administering (orally or by i.v.) a therapeutically effective amount of said drug.

731. Additionally, “inducing” the therapeutically effective blood levels is achieved by administering the therapeutically effective amount in any manner that operates via the blood, which includes oral and intravenous administration (both methods known in the prior art). This is confirmed both by the specification itself and arguments made by patent owner. The ’297 patent explains that “inducing plasma levels” of a therapeutic agent (netupitant) corresponds to administration of the therapeutic agent. EX1004 (’297 patent), 10:26-34 (“netupitant can be

administered in prodrug form, in which case the invention will provide a method of treatment by ***inducing plasma levels of netupitant***"); *id.* ("the plasma level of netupitant ***induced*** by the prodrug administration will ***correspond to the level attained by the administration*** of netupitant…in the doses and routes of administration described herein."). Additionally, when applying for "Patent Term Extension" for the '357 patent, I understand that Helsinn argued that ***administration*** of a prodrug form of netupitant corresponded with ***inducing*** the netupitant plasma levels. EX1006 (file history of '927 application), 461.

732. Thus, in sum, a person of ordinary skill in the art would have understood that "administering to said subject therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone" naturally satisfies the claimed "inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone" whenever the palonosetron and netupitant are delivered through the blood (i.e., when administration is accomplished orally or intravenously).

733. Herrstedt expressly discloses multiple studies administering to said subjects therapeutically effective amounts of a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist in a combination regimen with dexamethasone. Herrstedt summarizes multiple studies for antiemetic treatment of patients receiving highly emetogenic chemotherapy, wherein the antiemetic treatment is a triple-drug

combination comprising (i) a 5-HT_3 receptor antagonist (e.g., ondansetron), (ii) an NK_1 receptor antagonist (aprepitant), and (iii) dexamethasone. EX1010 (Herrstedt), 146 ("Two of the ***HEC*** studies used an identical design…***ondansetron***, ***dexamethasone*** and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes benefits to patients receiving the triple-drug antiemetic combination. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.").

734. Herrstedt teaches or suggests administering palonosetron as its 5-HT3 receptor antagonist. Herrstedt identifies palonosetron as a favorable 5-HT_3 receptor antagonist for treating emesis. EX1010 (Herrstedt), 146. Herrstedt specifically teaches palonosetron differed from other 5-HT_3 receptor antagonists because it showed beneficial properties "in the treatment of delayed emesis from MEC" and also had an order of magnitude increase in half-life as compared to the 5-HT_3 receptor antagonist ondansetron. *Id.*, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours); *see also id.*, 146 ("in the MEC studies some of the evaluable parameters ***significantly favoured palonosetron***."). Herrstedt further describes palonosetron as a suitable substitution for ondansetron

for treating emesis, stating: "Palonosetron has been compared to ondansetron and dolasetron in three randomized, double-blind trials" and each "demonstrated that palonosetron was not inferior to dolasetron and ondansetron." *Id.*, 146. Thus, a POSA would have had good reason to employ a therapeutically effective amount of the "significantly favoured" palonosetron as the 5-HT_3 receptor antagonist to said patient. Furthermore, the POSA would have had a reasonable expectation of success in making such a substitution because both palonosetron and ondansetron worked through an identical mechanism (i.e., 5-HT_3 receptor antagonism) to achieve the same therapeutic result (i.e., anti-emesis).

735. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of a therapeutically effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil

and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

736. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective dose.

737. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the

> regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18; *see id.*, 18 (SP-NK_1 receptor system known to have neuro-anatomical overlap with 5-HT family of receptors). Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's combination regimen with palonosetron and dexamethasone. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

738. Accordingly, Herrstedt discloses administering to said subject a therapeutically effective amount of a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist in a combination regimen with dexamethasone, Herrstedt suggests employing palonosetron as its 5-HT_3 receptor antagonist, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a

POSA had good reasons to use therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone for treatment of nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy, such as in the method disclosed in Herrstedt.

739. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in claim element 1(a).

740. The combination of Herrstedt and Bös thus teaches all of the elements of claim 1 and rendered the claim obvious as a whole.

B. Claim 2

> **2[pre].** A method of achieving complete response during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising

741. I have reproduced above the preamble of claim 2 of the ’297 patent. Herrstedt teaches a “method of achieving complete response during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy” as disclosed in the preamble of claim 2.

742. Herrstedt discloses a method for preventing “[c]hemotherapy-induced nausea and vomiting” in a subject receiving highly emetogenic cancer chemotherapy by administering an antiemetic drug combination. EX1010 (Herrstedt), 143; *id.*, 144 (“Most anti-emetic agents act by binding at one of these

receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy."), 146. Herrstedt describes administering its combination therapy to prevent nausea and vomiting "in patients ***receiving*** cisplatin-based, ***highly emetogenic chemotherapy***." *Id.*, 146.

743. Herrstedt describes achieving complete response during the acute and delayed phases. Herrstedt identifies that "***Complete response***, defined as 'no emesis and no rescue therapy on ***days 1-5*** postcisplatin', was ***the primary end-point in all studies***." EX1010 (Herrstedt), 146. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Thus, Herrstedt's defined "complete response" (including days 1-5) encompasses both the acute and delayed phases. Herrstedt summarizes that complete response was observed with its antiemetic combination:

> In the Hesketh study, a ***complete response*** of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen, and in the Poli-Bigelli study ***complete response*** rates were 62.7% versus 43.3%. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2-4. Again a statistical[] benefit favouring aprepitant was seen, resulting in a ***complete response*** in the aprepitant arm of 72.0% versus 60.6% in the control arm. In the first two studies, ***a difference of approximately 20% in complete response rates*** was seen.

EX1010 (Herrstedt), 146 (parentheticals and references omitted). Herrstedt discloses that further administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

744. The Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that complete response was achieved during the acute and delayed phases. Poli-Bigelli expressly confirms the antiemetic combination achieves complete response during both the acute phase and the delayed phase:

> In the ***assessments of complete response*** over specific periods after cisplatin, the aprepitant regimen provided a ***substantial improvement of 14 percentage points*** over standard therapy in the prevention of ***acute*** symptoms, and a ***highly remarkable improvement of about 21 percentage points*** in the prevention of ***delayed*** CINV.

EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Figure 2 (below).

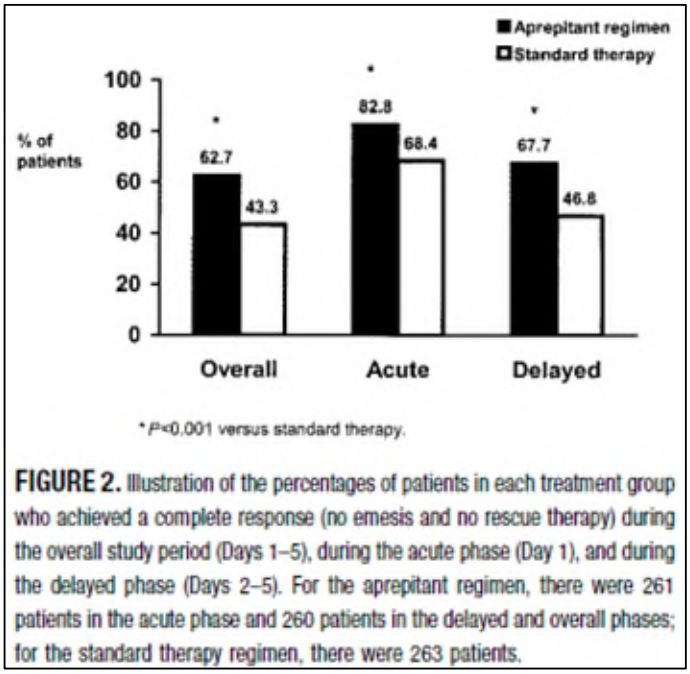


FIGURE 2. Illustration of the percentages of patients in each treatment group who achieved a complete response (no emesis and no rescue therapy) during the overall study period (Days 1–5), during the acute phase (Day 1), and during the delayed phase (Days 2–5). For the aprepitant regimen, there were 261 patients in the acute phase and 260 patients in the delayed and overall phases; for the standard therapy regimen, there were 263 patients.

Hesketh also confirms the dosing combination of Herrstedt achieves complete response during the acute and delayed phases. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

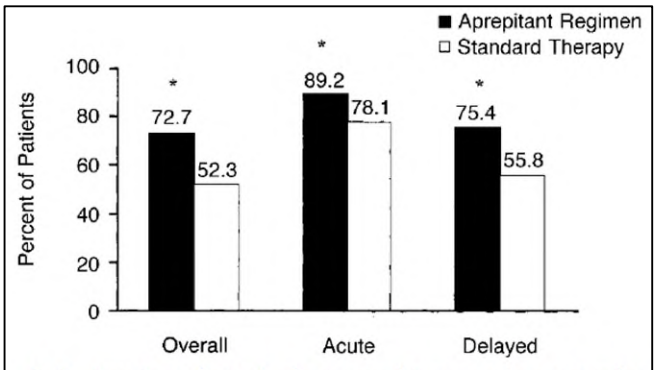


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *P < .001 versus standard therapy.

Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that complete response was achieved during the acute and delayed phases.

745. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 2.

> **2(a).** inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

746. I have reproduced above the inducing step (a) element of claim 2. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the inducing step of claim 2(a).

747. Claim element 2(a) is identical to claim element 1(a). For at least the same reasons discussed above (Section XX.A, claim element 1(a)), the combination of Herrstedt and Bös discloses administering to said subject therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone—which naturally satisfies "inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone." Accordingly, the combination of Herrstedt and Bös also discloses the subject matter recited in claim element 2(a).

748. The combination of Herrstedt and Bös thus teaches all of the elements of claim 2 and rendered the claim obvious as a whole.

C. Claim 3

3[pre]. A method of preventing nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising

749. I have reproduced above the preamble of claim 3 of the ’297 patent. Herrstedt teaches a “method of preventing nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising” as disclosed in the preamble of claim 2.

750. Herrstedt discloses a method for preventing “[c]hemotherapy-induced nausea and vomiting” in a subject receiving highly emetogenic cancer chemotherapy by administering an antiemetic drug combination. EX1010 (Herrstedt), 143; *id.*, 144 (“Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy.”), 146. Herrstedt describes administering its combination therapy to prevent nausea and vomiting “in patients ***receiving*** cisplatin-based, ***highly emetogenic chemotherapy***.” *Id.*, 146.

751. Herrstedt describes preventing nausea during the acute and delayed phases of chemotherapy. Herrstedt explains its triple combination antiemetic improves efficacy “against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy” and “is also active in the protection against ***delayed***

emesis." EX1010 (Herrstedt), Abstract. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Herrstedt describes studies treating nausea and vomiting with a triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

752. Poli-Bigelli expressly confirms administering the combination of Herrstedt prevents nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1039 (Poli-Bigelli), 3096-3097. For example, Poli-Bigelli describes prevention of nausea via improvement of complete response over periods including the acute and delayed phases, and also explains this parameter is a stand-in for the control of nausea:

> In the assessments of complete response over specific periods after cisplatin, the aprepitant regimen provided a ***substantial improvement*** of 14 percentage points over standard therapy in the prevention of ***acute*** symptoms, and a ***highly remarkable improvement*** of about 21 percentage points in the prevention of ***delayed*** CINV.
>
> Because patients were considered treatment failures if they either vomited or took rescue medication ***to alleviate nausea***, ***the complete response endpoint*** not only reflects control of emesis but also indirectly ***reflects control of nausea***.

EX1039 (Poli-Bigelli), 3096. Thus, although Poli-Bigelli did not directly evaluate nausea during the acute phase, a POSA would have understood the results of the study to nonetheless suggest Herrstedt's triple therapeutic combination to prevent nausea during both the acute and delayed phases. *Id.*, 3092 ("an acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Poli-Bigelli explains:

> Furthermore, the ***rates of no significant nausea and no nausea were consistently greater with the aprepitant regimen***. Moreover, for the more stringent endpoint of ***complete protection, which incorporated*** assessments for no emesis, no use of rescue, and ***no significant nausea*** (VAS score < 25 mm), the percentages of patients who achieved this endpoint were ***significantly greater in the aprepitant group for all 3 time periods evaluated***. The aprepitant group also achieved significantly greater success for the most stringent endpoint of total control, which incorporated ***a very rigorous nausea assessment*** (no nausea; VAS score < 5 mm) ***for the entire 5-day period*** after chemotherapy and ***especially for the delayed phase***.

Id., 3096; *see also id.*, 3093. Thus, Poli-Bigelli identified the addition of NK_1 receptor antagonist (aprepitant) as disclosed in Herrstedt's triple therapy combination prevented nausea during the acute phase of chemotherapy induced nausea and vomiting, and especially during the delayed phase of chemotherapy induced nausea and vomiting.

753. Hesketh also confirms administering the combination of Herrstedt prevents nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1037 (Hesketh), 4116-4117. As with Poli-Bigelli, Hesketh explains that Herrstedt's triple therapy combination improved complete response during both acute and delayed phases and that this directly indicated prevention of nausea:

> [T]he addition of a 3-day regimen of aprepitant significantly ***improved complete response*** as compared with standard therapy ***throughout the acute and delayed phases***. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant) was clearly ***both statistically significant and clinically meaningful***, and was particularly marked during the delayed phase…. Because patients were considered treatment failures if they had any emesis or took rescue medication ***to alleviate nausea***, the primary complete response end point not only reflected control of emesis, but also ***functioned as a surrogate index of nausea control***.

EX1037 (Hesketh), 4117. Regarding said complete response parameter, "[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (85.4% v 55.8%***; P < .001)." *Id.*, 4115; *see also id.*, Figure 2 (reproduced below).

754. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

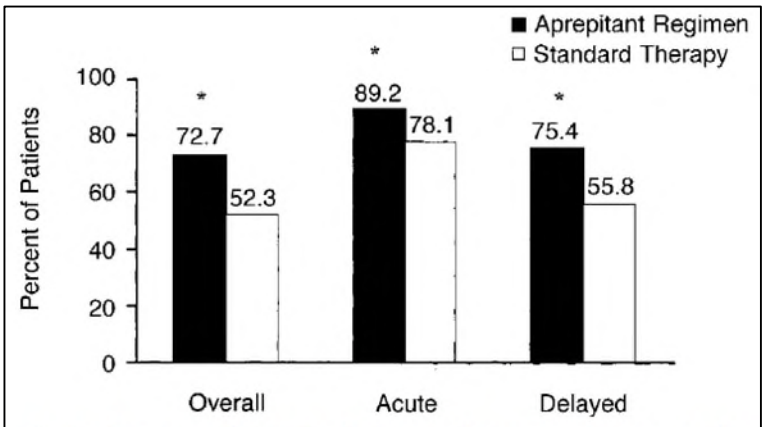


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *P < .001 versus standard therapy.

A POSA would therefore have understood, based on Hesketh's complete response results, that administration of Herrstedt's triple therapy combination prevents nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting. Indeed, Hesketh explains that Herrstedt's triple therapy combination ("aprepitant group") was overall superior to the standard therapy:

> Regardless of the specific end point, ***response rates overall and in the acute and delayed phases were consistently greater*** for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and ***complete protection*** (which ***incorporates both emesis and nausea assessment***), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were ***consistently numerically higher in the aprepitant group***. The higher response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, ***indicate that aprepitant provided some benefit against nausea as well as emesis***.

EX1037 (Hesketh), 4117. Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that administration of the triple therapy combination prevents nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting.

755. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 3.

> **3(a).** inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

756. I have reproduced above the inducing step (a) element of claim 3. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the inducing step of claim 3(a).

757. Claim element 3(a) is identical to claim element 1(a). For at least the same reasons discussed above (section XX.A, claim element 1(a)), the combination of Herrstedt and Bös discloses administering to said subject therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone—which naturally satisfies "inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone." Accordingly, the combination of Herrstedt and Bös also discloses the subject matter recited in claim element 3(a).

758. The combination of Herrstedt and Bös thus teaches all of the elements of claim 3 and rendered the claim obvious as a whole.

D. Claims 4, 13, 19

> **4.** The method of claim 1, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

> **13.** The method of claim 2, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy
>
> **19.** The method of claim 3, wherein said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

759. Claims 4, 13, and 19 each depends from independent claims 1, 2, and 3 (respectively) and additionally recites said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy.

760. As I previously addressed above, each of claims 1, 2, and 3 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.C, above.

761. Herrstedt teaches an effective amount of the antiemetic regimen is administered in conjunction with administering the chemotherapy. Herrstedt provides a summary of two studies employing the triple anti-emetic drug regimen described above. *See* Claim 1. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) and employing palonosetron as the 5-HT_3 receptor (disclosed in Herrstedt) with dexamethasone was an obvious anti-emetic regimen. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

762. A POSA reviewing Herrstedt would have understood that an effective amount of the antiemetic therapeutics is administered prior to the chemotherapy—in other words, said therapeutically effective blood levels of 5-HT_3 and NK_1 receptor antagonists are induced by the anti-emetic regimen administered prior to said chemotherapy. For example, Poli-Bigelli and Hesketh both expressly confirm that the antiemetic combination (NK_1 and 5-HT_3 receptor antagonists with dexamethasone) is administered prior to the emetogenic chemotherapy (e.g., cisplatin). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes prior to cisplatin***, all patients received ***ondansetron and dexamethasone***.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing the NK_1 receptor antagonist (aprepitant) and the 5-HT_3 receptor antagonist (ondansetron) with dexamethasone prior to the emetogenic chemotherapy (cisplatin) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes before cisplatin***, all patients received ***ondansetron*** (infused over 15 minutes) ***and dexamethasone***.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer the therapeutically effective amount of the antiemetic drug combination prior to the chemotherapy, and would have had a reasonable expectation of success that such dosing would provide relief from emesis.

763. As I explained above, it was obvious to employ netupitant as the NK_1 receptor antagonist and palonosetron as the 5-HT_3 receptor antagonist. Section XX.A, above (claim element 1[pre]). Furthermore, administering to a patient a therapeutically effective amount of palonosetron and netupitant results in inducing in said subject therapeutically effective blood levels of palonosetron and netupitant. Section XX.A, above (claim element 1(a)).

764. Herrstedt suggests its triple therapeutic combination can be administered as an intravenous anti-emetic regimen. With regard to palonosetron, Herrstedt indicates only intravenous administration was available at the time of its publication. EX1010 (Herrstedt), Table 3. Poli-Bigelli and Hesketh confirm the 5-HT_3 receptor antagonist of Herrstedt's anti-emetic regimen is administered intravenously. EX1039 (Poli-Bigelli), 3091 ("intravenous ondansetron 32 mg"); EX1037 (Hesketh), 4113 (same). With regard to aprepitant, Herrstedt suggests its NK_1 receptor antagonist can be administered intravenously. As noted above,

Herrstedt summarizes studies including Hesketh. Hesketh provides additional details, including that while aprepitant was administered in its study in oral form, another study observed the same antiemetic effect with "its ***intravenously administered*** prodrug." EX1037 (Hesketh), 4118. Additionally, Bös teaches that, with regard to its NK_1 receptor antagonists—including netupitant—the compounds can be "in the form of pharmaceutical compositions" and administration includes "***parenterally***, e.g. in the form of ***injection solutions***." EX1014 (Bös), 40:52-62. A skilled practitioner would have known that intravenous administration was a common form of parenterally administered medications. *See, e.g.*, EX1050 (Merriam-Webster) (parenteral is administration "occurring outside the intestine" including "administration by intravenous, intramuscular, or subcutaneous injection."). It is therefore my opinion that Bös suggests intravenous administration of netupitant. Finally, with regard to dexamethasone, Herrstedt explained that corticosteroids (e.g., dexamethasone) were administered either intravenously or orally. EX1010 (Herrstedt), 146-147; *see also* EX1013 (MASCC), Tables 3-4 (confirming oral and intravenous dexamethasone).

765. A skilled practitioner would have had good reason to administer each of the therapeutic drugs intravenously. For example, administration intravenously avoids first pass metabolism, resulting in more consistently administered therapeutic and avoiding metabolic degradation. *See, e.g.*, EX1046 (Thummel),

3173 (“When a drug is dosed intravenously, it avoids first-pass metabolism and is generally completely bioavailable to the different tissues of the body.”). It was known that “[f]irst-pass metabolism is a common cause of incomplete and variable absolute bioavailability for an orally dosed drug” and “[t]he drug-metabolizing enzyme CYP3A4 is often implicated in this process.” *Id.*, Abstract. As I described above, the skilled practitioner would have reasonably expected each of netupitant and dexamethasone to be substrates of CYP3A4. *See* Section XIX.C, above. Additionally, Herrstedt explains palonosetron is also a substrate of CYP3A4. EX1010 (Herrstedt), 147. Therefore there was good reason to administer each of the therapeutic agents intravenously.

766. The POSA would have understood it was routine to administer the therapeutic agents intravenously. The skilled artisan would have understood that it was routine practice to formulate therapeutic agents in various ways, including intravenously, and that formulating the therapeutic agents for intravenous administration required nothing more than routine experimentation. EX1059 (Li), Abstract, 12-13. Indeed, intravenous formulations are typically one of the first forms of therapeutic delivery developed. *Id.*, 3 & Table 1 (“oral and intravenous administration” recommendations for animal models). The ’297 patent admits it was within the skilled practitioner’s ability to develop such intravenous administrations. The ’297 patent specification never discloses intravenously

administered netupitant, palonosetron, or dexamethasone. Instead, insofar as the '297 specification describes intravenous administration, it is solely to state—in full—that:

> Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

EX1004 ('297 patent), 10:35-39. A person of ordinary skill in the art would have understood from the '297 specification's threadbare disclosure that it was within the POSA's own ability to develop and administer such intravenous formulation.

767. Thus, it is my opinion that each of claims 4, 13, and 19 as a whole was also obvious over Herrstedt and Bös.

E. Claims 8-10

> **8.** The method of claim 1, wherein said method achieves complete response in said subject.
>
> **9.** The method of claim 1, wherein said method achieves no emesis in said subject.
>
> **10.** The method of claim 1, wherein said method achieves no rescue medication in said subject.

768. Each of claims 8-10 depends from independent claim 1. Claim 8 additionally recites the method achieves complete response in said subject. Claim 9 additionally recites the method achieves no emesis in said subject. Claim 10 additionally recites the method achieves no rescue medication in said subject.

769. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XX.A, above.

770. As Herrstedt explains, "complete response" is defined as "no emesis and no rescue therapy." EX1010 (Herrstedt), 146. The detailed studies summarized in Herrstedt—Poli-Bigelli and Hesketh—confirm this definition. EX1039 (Poli-Bigelli), 3093 ("For the primary endpoint of complete response (no emesis and no use of rescue therapy), the aprepitant regimen was statistically superior."); EX1037 (Hesketh), 4113 ("The primary end point for the efficacy analysis was the proportion of patients with complete response, defined as no emetic episodes and no rescue therapy."). This is also consistent with the '297 patent. EX1004 ('297 patent), 18:10-11 ("The primary efficacy endpoint was the complete response rate (defined as no emetic episodes, no rescue medication).") Thus, a POSA would have understood that a method that achieves complete response in a patient (claim 8) also achieves no emesis in the patient (claim 9) and no rescue medication in the patient (claim 10), because any use of rescue medication or emesis would by definition mean that there was not complete response.

771. Herrstedt discloses the administration of the triple antiemetic combination achieves complete response in patients, and that complete response is the primary end-point in its studies. Herrstedt explains that, following chemotherapy, "***[c]omplete response***, defined as 'no emesis and no rescue therapy

on days 1-5 postcisplatin', was the ***primary end-point in all studies***." EX1010 (Herrstedt), 146. Herrstedt explains that the "***complete response***" includes both patients "with no emesis" (i.e., no emetic episodes) and "without the need of rescue anti-emetics" (i.e., no use of rescue medication). *Id.*

772. As I explained above (Section XX.A, Claim 1) Herrstedt describes studies treating nausea and vomiting with a therapeutically effective amount of its triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. Poli-Bigelli expressly confirms Herrstedt's achievement of complete response in the patients. EX1039 (Poli-Bigelli), 3092 (following chemotherapy, the "proportion of patients who ***achieved a complete response*** (defined as no emetic episodes and no use of rescue therapy) in the overall study period (Days 1-5) was ***the primary endpoint of the efficacy analysis***."); *id.*, 3093 ("For the primary endpoint of ***complete response*** (no emesis and no use of rescue therapy, the aprepitant regimen was ***statistically superior*** to standard therapy in the overall study period (***62.7% vs. 43.3% in the overall phase***, a 19 percentage-point difference; $P < 0.001$), as well in the separate analyses of the acute phase (***82.8% vs. 68.4%***; $P < 0.001$), and particularly in the delayed phase (***67.7% vs. 46.8%***; $P < 0.002$)."); *see also id.*, Figure 2 (reproduced below).

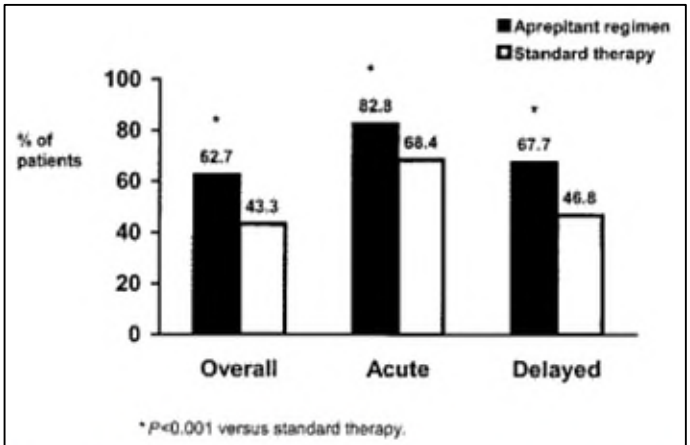


FIGURE 2. Illustration of the percentages of patients in each treatment group who achieved a complete response (no emesis and no rescue therapy) during the overall study period (Days 1–5), during the acute phase (Day 1), and during the delayed phase (Days 2–5). For the aprepitant regimen, there were 261 patients in the acute phase and 260 patients in the delayed and overall phases; for the standard therapy regimen, there were 263 patients.

773. Hesketh also confirms the dosing combination of Herrstedt achieves complete response in the patient. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was ***significantly higher*** in the aprepitant group (***72.7% [n = 260] v 52.3***% in the standard therapy group [n = 260]), as were the percentages on day 1, and especially on days 2 to 5." EX1037 (Hesketh), Abstract. Hesketh explains improvement was seen with the administered triple antiemetic therapy described in Herrstedt:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was ***superior*** to standard therapy overall (days 1 to 5; ***72.7% v 52.3%***; P < .001), as well as in separate analyses of both the acute phase (***89.2% v 78.1%***; P < .001), and even more notably, the delayed phase

(***75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

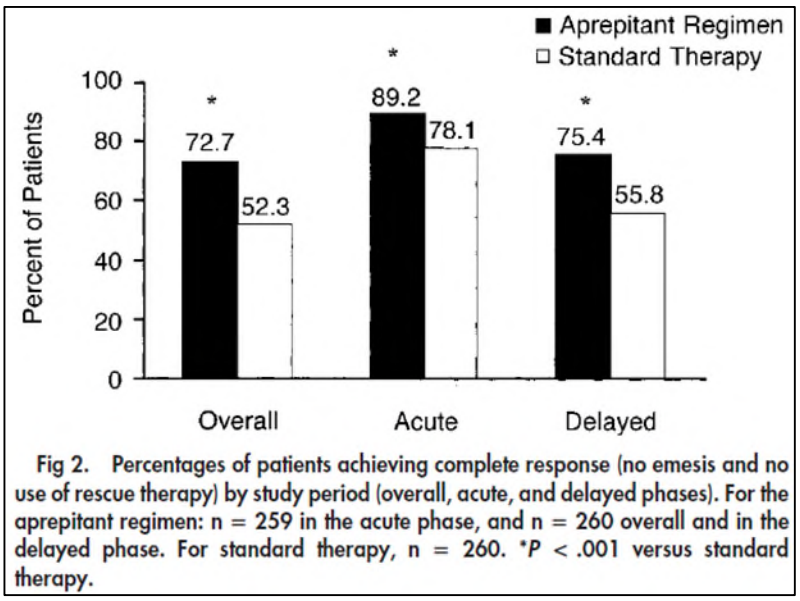


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *P < .001 versus standard therapy.

774. Poli-Bigelli and Hesketh also separately and explicitly confirm Herrstedt's achievement of no emesis in the patients. Poli-Bigelli explains that:

> The percentage of patients in the aprepitant group who had ***no emesis was significantly greater*** compared with the standard therapy group for all three phases of the study.

EX1039 (Poli-Bigelli), 3093. Poli-Bigelli provides details in a table illustrating a statistically significant greater number of patients achieving no emesis after administration of Herrstedt's triple therapy antiemetic in all measured phases. *See id.*, Table 2 (reproduced below):

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Hesketh similarly observed that "for the end points of no emesis…the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV." EX1037 (Hesketh), 4117. Hesketh also provides details in a table illustrating the statistically significant greater number of patients achieving no emesis after administration of Herrstedt's triple therapy antiemetic in all measured phases. *See id.*, Table 2 (reproduced below):

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.
*$P < .05$ versus standard therapy (significance based on logistic regression model).
†$P < .01$ versus standard therapy (significance based on logistic regression model).
‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.
§Analysis not planned.

775. Poli-Bigelli and Hesketh also separately and explicitly confirm Herrstedt's achievement of no rescue medication in the patients. Hesketh explains that the "aprepitant regimen was also ***statistically superior*** in all comparisons for the secondary and exploratory end points of no emesis, ***no rescue therapy***, and ***complete protection***." EX1037 (Hesketh), 4115. Hesketh describes that the "***significantly less frequent need for rescue therapy***, indicate[s] that aprepitant provided some benefit against nausea as well as emesis." *Id.*, 4117. Hesketh provides details in a table illustrating the statistically significant greater number of patients achieving no rescue medication after administration of Herrstedt's triple therapy antiemetic in all measured phases. *See id.*, Table 2 (reproduced below):

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

Poli-Bigelli similarly provides details in a table that illustrates statistically significantly greater number of patients achieved no rescue medication after

Herrstedt's triple therapy antiemetic was administered, and that this was true for all measured phases. EX1039 (Poli-Bigelli), Table 2 (reproduced below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

776. A POSA would reasonably have expected the combination of Herrstedt, as modified in view of Bös to include netupitant along with palonosetron and dexamethasone, to provide similarly effective treatment, including complete response without emesis or need of rescue medication. Accordingly, it is my opinion that each of claims 8-10 as a whole was also obvious over Herrstedt and Bös.

F. Claims 11, 17

11. The method of claim 1, wherein said method prevents nausea in said subject.

17. The method of claim 2, wherein said method prevents nausea in said subject.

777. Claims 11 and 17 each depends from independent claims 1 and 2, respectively. Each of claims 11 and 17 additionally recites the method prevents nausea in said subject.

778. As I previously addressed above, each of claims 1 and 2 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.B, above.

779. Herrstedt discloses a regimen for treating chemotherapy-induced nausea and vomiting and that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was effective to prevent nausea in patients. For example, Herrstedt describes its antiemetic dosing combination achieved improvement in the primary endpoint of "complete response," which requires no use of rescue therapy (e.g., for treatment of nausea).

780. Poli-Bigelli expressly confirms Herrstedt's antiemetic dosing regimen prevents nausea in patients. Poli-Bigelli reports that "the rates of no significant nausea and no nausea were ***consistently greater*** with the aprepitant regimen" disclosed in Herrstedt. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Additionally, Poli-Bigelli teaches that "[b]ecause patients considered treatment failures if they either vomited or took rescue medication to alleviate nausea, the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli explains that Herrstedt's therapeutic regimen prevents nausea in subjects.

781. Hesketh also confirms the antiemetic dosing combination of Herrstedt prevents nausea in subjects. Hesketh explains that Herrstedt's therapeutic combination achieves complete response in patients (Section XX.E, above (claim 8)) and "[b]ecause patients were considered treatment failures if they had any emesis or took rescue medication to alleviate nausea, the primary complete response end point not only reflected control of emesis, but also functioned as a

surrogate index of ***nausea control***." EX1037 (Hesketh), 4117. Thus, Hesketh's achievement of complete control supports that there was prevention of nausea in subjects. Hesketh also evaluated nausea as its own measurable parameter and stated that:

> Although the groups did not differ statistically for total control, no nausea, and no significant nausea, ***rates for these end points were consistently numerically higher in the aprepitant group***. The higher response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, indicate that aprepitant provided ***some benefit against nausea*** as well as emesis.

Id., 4117; *see also id.*, Table 2 (reproduced below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

As Hesketh reports, there is a consistent decrease of nausea through all time groups for subjects receiving Herrstedt's therapeutic combination. Thus, Hesketh further supports that Herrstedt's triple therapeutic method prevents nausea in subjects.

782. Accordingly, it is my opinion that each of claims 11 and 17 as a whole was also obvious over Herrstedt and Bös.

G. Claims 12, 18, 23

> **12.** The method of claim 1, wherein said blood levels of netupitant are independently effective to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy.
>
> **18.** The method of claim 2, wherein said blood levels of netupitant are independently effective to produce complete response in a subject receiving highly emetogenic cancer chemotherapy.
>
> **23.** The method of claim 3, wherein said blood levels of netupitant are independently effective to prevent nausea in a subject receiving highly emetogenic cancer chemotherapy.

783. Claims 12, 18, and 23 each depends from independent claims 1, 2, and 3, respectively. Each of claims 12, 18, and 23 additionally recites said blood levels of netupitant are independently effective to prevent or produce an effect. In claim 12, it is to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy. In claim 18, it is to produce complete response in a subject receiving highly emetogenic cancer chemotherapy. In claim 23, it is to prevent nausea in a subject receiving highly emetogenic cancer chemotherapy.

784. As I previously addressed above, each of claims 1, 2, and 3 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.C, above.

785. As an initial matter, I note the ’297 patent specification does not define or otherwise disclose what is meant by “independently effective.” From my review of the file history of the ’297 patent, the first mention of netupitant being “independently effective” was in a June 1, 2018, amendment adding new claims. EX1008 (file history of ’050 application), 76-80. During prosecution of the application that issued as the ’515 patent, the patent applicant indicated that independent effectiveness can be shown by, e.g., demonstrating additive effect in a multi-drug administration. The patent applicant stated that:

> The Examiner might be suggesting that other drugs can be administered during the five-day period, but that argument misses the point. Table 5 in the specification shows that a single 300 mg dose of netupitant ***independently provides*** protection against nausea and vomiting for five consecutive days, regardless of whether other drugs are administered.

EX1007 (file history of ’327 application), 329. That the patent applicant treats “independent effect” as something demonstrating an additive effect in a multiple drug administration was further shown in prosecution of that same application. Discussing Table 5 from the patent specification, the patent applicant argued that:

> Table 5 reports the results of a study comparing palonosetron alone to three different combinations of netupitant and palonosetron, as well as to the combination of aprepitant and ondansetron. ***By comparing the combination of palonosetron + netupitant to the single administration of palonosetron,***[5] ***one is able to determine whether netupitant is having an independent effect on the measured parameter***.

EX1007 (file history of '327 application), 201. Thus, it was the patent applicant's contention that "independent effect" was shown by observing the ***additional*** effect provided by netupitant when ***added to*** the standard therapy.

786. Herrstedt discloses that a therapeutically effective amount of its NK_1 receptor antagonist is independently effective to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy. In other words, Herrstedt's NK_1 receptor antagonist further prevents acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy as compared to the standard therapeutic combination without the

[5] What Table 5 refers to as "palonosetron + netupitant" also includes dexamethasone. EX1004 ('297 patent), 17:28-39 (Groups 2-4). Likewise, what the table refers to as "palonosetron alone" includes dexamethasone. *Id.*, 17:25-27 (Group 1).

NK_1 receptor antagonist. Herrstedt describes its trials of aprepitant are conducted "in patients receiving ***cisplatin***-based, ***highly emetogenic chemotherapy***." Herrstedt describes its triple therapy combination (5-HT_3 receptor antagonist, dexamethasone, and NK_1 receptor antagonist) is recommended "for ***prevention of acute and delayed nausea and vomiting***." *Id.*, 148 & Table 4 (MASCC guidelines). Herrstedt explicitly teaches improved effectiveness to treat both nausea and vomiting with the triple therapy (NK_1 receptor antagonist, 5-HT_3 receptor antagonist, and corticosteroid) ***as compared to*** the corresponding combination without the NK_1 receptor antagonist. EX1010 (Herrstedt), 146. The POSA would have understood that the addition of NK_1 receptor antagonist increased overall efficacy of the therapy. Herrstedt discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

787. Poli-Bigelli expressly confirms Herrstedt's antiemetic dosing regimen prevents acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy (cisplatin). Poli-Bigelli reports that "the rates of no significant nausea and no nausea were ***consistently greater*** with the aprepitant regimen" disclosed in Herrstedt. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Additionally, although Poli-Bigelli indicates "analysis not performed" for acute nausea, Poli-Bigelli teaches that "[b]ecause patients considered treatment failures if they either vomited or took rescue medication to alleviate nausea, ***the complete response*** endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination ***improved complete response*** by 14 percentage points during the acute period, and "a ***highly remarkable improvement*** of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096; *id.*, Abstract (Overall complete response: 62.7% (aprepitant), 43.3% (standard group); Day 1 complete response: 82.8% (aprepitant), 68.4% (standard group); Days 2-5 complete response: 67.7% (aprepitant), 46.8% (standard group)). With regard to vomiting, Poli-Bigelli reports the "percentage of patients in the aprepitant group who had ***no emesis was significantly greater*** compared with the standard therapy group ***for all three phases of the study***" (i.e., overall, acute, and delayed phases). EX1039 (Poli-

Bigelli), 3093; *see also id.*, Table 2 (above). Thus, Poli-Bigelli shows that Herrstedt's antiemetic triple combination therapy (including NK_1 receptor antagonist) improves prevention of acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy as compared to the antiemetic therapy without NK_1 receptor antagonist, providing independent efficacy.

788. Hesketh also confirms the antiemetic dosing combination of Herrstedt prevents acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy (cisplatin). Hesketh explains that Herrstedt's therapeutic combination achieves complete response in patients (Section XX.E, above (claim 8)) and "[b]ecause patients were considered treatment failures if they had any emesis or took rescue medication to alleviate nausea, the primary complete response end point not only reflected control of emesis, but also functioned as a surrogate index of ***nausea control***." EX1037 (Hesketh), 4117. Thus, Hesketh's achievement of complete control supports that there was prevention of nausea in subjects. Hesketh also evaluated nausea as its own measurable parameter and stated that:

> Although the groups did not differ statistically for total control, no nausea, and no significant nausea, ***rates for these end points were consistently numerically higher in the aprepitant group***. The higher response rates of these end points in the aprepitant group, interpreted

in the context of a significantly less frequent need for rescue therapy, indicate that aprepitant provided ***some benefit against nausea*** as well as emesis.

Id., 4117; *see also id.*, Table 2 (reproduced below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
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NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

With regard to vomiting, Hesketh shows significant prevention of emesis in subjects receiving the NK_1 receptor antagonist combination. EX1037 (Hesketh), Table 2 (above). Thus, Hesketh shows that Herrstedt's antiemetic triple combination therapy (including NK_1 receptor antagonist) improves prevention of acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy as compared to the antiemetic therapy without NK_1 receptor antagonist, providing independent efficacy.

789. Because Herrstedt's study shows improved prevention of acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer

chemotherapy (e.g., claim 12), it also shows improved prevention of nausea in a subject receiving highly emetogenic cancer chemotherapy (e.g., claim 23). The therapeutically effective amount of the antiemetic triple combination therapy (including NK_1 receptor antagonist) improves prevention of acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy as compared to the antiemetic therapy without NK_1 receptor antagonist, providing independent efficacy. I also explained above (Section XX.E, Claim 8) that Herrstedt's triple combination antiemetic provided improved complete response the subjects receiving highly emetogenic cancer chemotherapy. Accordingly, Herrstedt describes its therapeutic dose of NK_1 receptor antagonist is independently effective to produce the effects claimed in each of claims 12, 18, and 23. Additionally, as I explained above, a POSA would have understood that administering a therapeutic effective amount of Herrstedt's antiemetic combination provided the blood levels of the therapeutic agents. *See* Sections XX.A-XX.C, above (claims 1-3). Finally, the POSA would have had good reason to employ Bös' second generation NK_1 receptor (netupitant) in Herrstedt's triple antiemetic combination because it was known to be a potent and selective NK_1 receptor antagonist. *See* Sections XX.A-XX.C, above (claims 1-3). Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both

compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

790. Accordingly, it is my opinion that each of claims 12, 18, and 23 as a whole was also obvious over Herrstedt and Bös.

H. Motivation to Combine

791. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy, to achieve complete response during the acute and delayed phases of chemotherapy induced nausea and vomiting in the subject receiving highly emetogenic cancer chemotherapy, and to prevent nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting in the subject receiving highly emetogenic cancer chemotherapy. The POSA would have achieved such effects by inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone. *See* Sections XX.A-XX.C, above. I described that persons having ordinary skill in the art would have had good reason to treat patients receiving highly emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt triple therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 and

NK_1 receptor antagonists administered with dexamethasone provided antiemetic effect). Additionally, I explained that a person having ordinary skill in the art would have modified the Herrstedt triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron.

792. The person having ordinary skill in the art also would have modified the Herrstedt triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Sections XX.A-XX.C, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify

Herrstedt by replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

793. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

I. Reasonable Expectation of Success

794. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt triple active combination therapy with the claimed netupitant and palonosetron therapeutics. *See* Sections XX.A-XX.C, above. I explained, for example, that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome.

795. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant)

would work in the same manner to achieve a similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant. Additionally, because each of the drugs in Herrstedt's triple combination targets a different mechanism providing relief for a patient suffering from nausea and vomiting, a POSA would have had a reasonable expectation of success in further improving both nausea and vomiting following CINV during both the acute and delayed period when the triple therapy was administered.

796. Accordingly, the POSA had good reason to combine Herrstedt and Bös to arrive at the claimed invention, and the POSA would have had a reasonable

expectation of success in making the modifications to arrive at the claimed invention.

XXI. ['297 PATENT GROUND 2] '297 PATENT CLAIMS 5-6, 14-15, AND 20-21 WERE OBVIOUS OVER HERRSTEDT, BÖS, AND ALOXI

797. For the reasons discussed in detail below, it is my opinion that claims 5-6, 14-15, and 20-21 of the '297 patent were obvious as a whole. The obviousness of claims 5-6, 14-15, and 20-21 is exemplified by disclosures in the Herrstedt, Bös, and Aloxi references.

798. I have evaluated below whether the combination of Herrstedt, Bös, and Aloxi discloses each and every element of each of claims 5-6, 14-15, and 20-21 of the '297 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claims 5, 14, 20

> **5.** The method of claim 1, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.
>
> **14**. The method of claim 2, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels

induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

20. The method of claim 3, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

799. Claims 5, 14, and 20 each depends from independent claims 1, 2, and 3 (respectively) and additionally recites ***(a)*** said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and ***(2)*** said blood levels are equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

800. As I previously addressed above, each of claims 1, 2, and 3 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.C, above.

801. Claim limitation (a) from each of claims 5, 14, and 20 ("said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy") is identical to the claim limitation of claims 4, 13, and 19. I explained above that each of claims 4, 13, and 19 was obvious over the combination of Herrstedt and Bös. *See* Section XX.D, above. For at least the same reasons, each of claim limitation 5(a), 14(a), and 20(a) was obvious over the combination of Herrstedt and Bös.

802. Herrstedt discloses that the therapeutically effective amount (clinical dose) of palonosetron is within the range of about 0.075 to about 1.0 mg. Herrstedt discloses, in Table 3, that it was known in the art to administer palonosetron in a 0.25 mg intravenous dose.

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

EX1010 (Herrstedt), Table 3.

803. Aloxi confirms that the POSA would select a dose equivalent to from 0.075 mg to 1.0 mg palonosetron hydrochloride administered orally. *See generally* Aloxi (testing 0.25 mg, 0.5 mg, and 0.75 mg palonosetron). Aloxi teaches oral palonosetron HCl capsules available and approved by the FDA for antiemetic treatment containing 0.56 mg palonosetron HCl, corresponding with 0.50 mg of the free base of palonosetron. EX1015 (Aloxi), 3. Aloxi thus explicitly discloses a palonosetron dose squarely in the center of the claimed range from the range of 0.075 mg to 1.0 mg.

804. Bös teaches that a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—are in a range that includes 50 to 500 mg of netupitant free base. Bös discloses a dose range for its NK_1 receptor antagonists

(including netupitant) that encompasses the claimed range from 50 to 500 mg. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

805. It is my opinion that a POSA would have recognized Bös' range spanning two orders of magnitude (about 10 to 1,000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts. It is my opinion that the POSA would have had good reason to optimize Bös' range when determining the therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22; Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

806. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the

’297 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the ’297 patent specification. *See, e.g.*, EX1004 (’297 patent), 7:54-60 (“The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure.”). Therefore, the ’297 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the dose equivalent to 50 to 500 mg of netupitant free base. Thus, it is my opinion that the POSA would have had good reason to select a range including from 50 to 500 mg when determining the therapeutically effective amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

807. A skilled artisan would have known to formulate the intravenous administrations to achieve blood levels equivalent to blood levels of palonosetron and netupitant as described by Herrstedt, Bös, and Aloxi. As I explained above (Section XX.A), it was routine to formulate intravenous administrations, and formulating the therapeutic agents for intravenous administration required nothing more than routine experimentation. EX1059 (Li), Abstract, 12-13. Adjusting dose levels was nothing more than optimization, and the POSA would have good reason to match the equivalent blood levels vetted from other sources—i.e., the 50-500

mg of netupitant (described by Bös, as explained above) and the 0.075-1.0 mg of palonosetron (described by Herrstedt and Aloxi, as explained above). The ’297 patent admits it was within the skilled practitioner’s ability to develop such formulations. The ’297 patent specification never discloses intravenously administered netupitant or palonosetron that achieves blood levels equivalent to the claimed dose ranges. Instead, insofar as the ’297 specification describes intravenous administration, it is solely to state—in full—that:

> Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

EX1004 (’297 patent), 10:35-39. When discussing the specific doses (0.075 to 1.0 mg of palonosetron, 50 to 500 mg netupitant), the ’297 patent describes this as an oral dose. *Id.*, 10:14-25. A person of ordinary skill in the art would have understood from the ’297 specification’s threadbare disclosure that it was within the POSA’s own ability to develop and administer such intravenous formulation that provides blood levels equivalent to blood levels induced known therapeutic amounts—i.e., equivalent to blood levels induced by 50 to 500 mg of netupitant free base and 0.075 to 1.0 mg palonosetron hydrochloride administered orally.

808. Accordingly, it is my opinion that each of claims 5, 14, and 20 as a whole was obvious over the combination of Herrstedt, Bös, and Aloxi.

B. Claims 6, 15, 21

> **6.** The method of claim 1, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.
>
> **15**. The method of claim 2, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.
>
> **21**. The method of claim 3, wherein (a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

809. Claims 6, 15, and 21 each depends from independent claims 1, 2, and 3 (respectively) and additionally recites said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy, and (2) said blood levels are equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

810. As I previously addressed above, each of claims 1, 2, and 3 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.C, above.

811. Claim limitation (a) from each of claims 6, 15, and 21 ("said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy") is identical to the claim limitation of claims 4, 13, and 19. I

explained above that each of claims 4, 13, and 19 was obvious over the combination of Herrstedt and Bös. *See* Section XX.D, above. For at least the same reasons, each of claim limitation 5(a), 14(a), and 20(a) was obvious over the combination of Herrstedt and Bös.

812. Aloxi discloses palonosetron is orally administered as palonosetron hydrochloride, and the therapeutically effective amount of said palonosetron hydrochloride is about 0.56 mg of palonosetron hydrochloride. Aloxi capsules contained 0.56 mg palonosetron HCl formulated for oral administration and indicated for the prevention of acute nausea and vomiting following initial and repeat courses of moderately emetogenic chemotherapy. EX1015 (Aloxi), 1-4; *id.*, 3 ("Each light beige opaque soft gelatin ALOXI Capsule ***contains 0.56 mg of palonosetron HCl*** equivalent to palonosetron 0.5 mg."). The POSA would have had good reason to formulate an administration of palonosetron HCl to achieve equivalent blood levels to the FDA approved palonosetron HCl dose (0.56 mg). The POSA also would have had a reasonable expectation of success in achieving the desired therapeutic result by administering the equivalent to this known and approved therapeutic amount because the specific dose had gone through the rigors of FDA approval.

813. Bös teaches a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of oral administration a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

814. It would have been routine for a POSA in view of the disclosures of Herrstedt and Bös to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11

("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating CINV.

815. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '297 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '297 patent specification. *See, e.g.*, EX1004 ('297 patent), 7:54-60 ("The skilled artisan will be able to determine appropriate dosages depending on these and other factors in addition to the present disclosure."). Therefore, the '297 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose equivalent to 300 mg when determining the therapeutically effective amount of netupitant to administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

816. The ’297 patent itself does not ascribe any particular or unexpected results associated with the 0.56 mg palonosetron hydrochloride or the 300 mg dose of netupitant. I have reviewed the ’297 patent and do not observe any particular benefits linked with a 0.56 mg dose of palonosetron HCl or with a 300 mg dose of netupitant or with specifically. For example, the specification explains that 0.5 mg of palonosetron was selected for inclusion into a formulation, and that the 0.56 mg of palonosetron corresponded with 0.5 mg free base, but does not explain this dose of palonosetron to be better than any others. EX1004 (’297 patent), 13:61-14:28. Therefore, based on my review of the ’297 patent, there is no particular or unexpected benefit ascribed specifically to an equivalent of the 0.56 mg dose of palonosetron hydrochloride. Similarly with regard to netupitant, the netupitant-dexamethasone drug interaction study (EX1004 (’297 patent), 16:1-40) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* EX1004 (’297 patent), Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 16:41-67), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant)

iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’297 patent, there is no particular or unexpected benefit ascribed to the 0.56 mg dose of palonosetron hydrochloride or the 300 mg dose of netupitant specifically.

817. A skilled artisan would have known to formulate the intravenous administrations to achieve blood levels equivalent to blood levels of palonosetron and netupitant as described by Bös, and Aloxi. As I explained above (Section XX.A), it was routine to formulate intravenous administrations, and formulating the therapeutic agents for intravenous administration required nothing more than routine experimentation. EX1059 (Li), Abstract, 12-13. Adjusting dose levels was nothing more than optimization, and the POSA would have good reason to match the equivalent blood levels vetted from other sources—i.e., the 300 mg of netupitant (described by Bös, as explained above) and the 0.56 mg of palonosetron hydrochloride (described by Herrstedt and Aloxi, as explained above). The ’297 patent admits it was within the skilled practitioner’s ability to develop such formulations. The ’297 patent specification never discloses intravenously administered netupitant or palonosetron that achieves blood levels equivalent to the claimed dose ranges. Instead, insofar as the ’297 specification describes intravenous administration, it is solely to state—in full—that:

> Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can

> be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

EX1004 (’297 patent), 10:35-39. When discussing the 0.56 mg dose of palonosetron hydrochloride, the ’297 patent specification describes this as an oral dose. *Id.*, 14:5-28. Likewise, when discussing the 300 mg dose of netupitant, the ’297 patent specification describes this as an oral dose. *Id.*, 16:1-40 (Example 3, “oral Netupitant”), 16:42-67 (Example 4, “netupitant as a single oral dose”), 17:37-39 (Example 5, “oral netupitant”). A person of ordinary skill in the art would have understood from the ’297 specification’s threadbare disclosure that it was within the POSA’s own ability to develop and administer such intravenous formulation that provides blood levels equivalent to blood levels induced known therapeutic amounts—i.e., equivalent to blood levels induced by 300 mg of netupitant free base and 0.56 mg palonosetron hydrochloride administered orally.

818. Accordingly, it is my opinion that each of claims 6, 15, and 21 as a whole was obvious over the combination of Herrstedt, Bös, and Aloxi.

C. Motivation to Combine

819. As I explained above (Sections XX.A, XX.H), persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös’ NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and

antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases.

820. The persons having ordinary skill in the art also would have been motivated to administer palonosetron in a formulation that provided the same efficacy (e.g., blood levels) of palonosetron HCl that was achieved with the FDA approved oral formulation. Aloxi describes an FDA-approved oral capsule of palonosetron HCl that was shown to provide antiemetic effect when administered to patients receiving emetogenic chemotherapy. EX1015 (Aloxi), 2-4. Thus, the POSA would have had good reason to use the Aloxi capsule of palonosetron HCl as a reference when developing an injectable version for its administration of palonosetron. *See* Sections XX.A, XX.H, above.

D. Reasonable Expectation of Success

821. As I explained above (Sections XX.A, XX.I), persons having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome. Similarly, I explained above that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant)

would work in the same manner to achieve similar (or improved) outcome. Sections XX.A, XX.I, above. The POSA also would have had a reasonable expectation of success in employing the dose amount disclosed by Aloxi, which had undergone the rigor of FDA approval, as I explain above. Sections XXI.A-XXI.B.

822. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXII. ['297 PATENT GROUND 3] '297 PATENT CLAIMS 7, 16, AND 22 WERE OBVIOUS OVER HERRSTEDT, BÖS, AND HARGREAVES

823. For the reasons discussed in detail below, it is my opinion that each of claims 7, 16, and 22 of the '297 patent was obvious as a whole. The obviousness of claims 7, 16, and 22 is exemplified by disclosures in the Herrstedt, Bös, and Hargreaves references.

824. I have evaluated below whether the combination of Herrstedt, Bös, and Hargreaves discloses each and every element of each of claims 7, 16, and 22 of the '297 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of

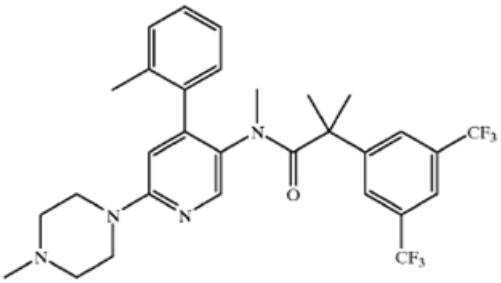
success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

825. As a high-level summary, Herrstedt discloses methods of treating both nausea and vomiting for five consecutive days in patients in need thereof. EX1010 (Herrstedt), 143, 146. Herrstedt also describes administering to the patient on day one an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt discloses administering to the patient on day one a therapeutically effective amount of a 5-HT_3 receptor antagonist (EX1010 (Herrstedt), 146) and teaches that palonosetron is a new 5-HT_3 receptor antagonist (*Id.*). Herrstedt also discloses administering to the patient on day one a first dose of dexamethasone in a lower dose than what would typically be given (i.e., ineffective against CINV when administered alone) but was effective when administered as discussed in Herrstedt's combination therapy. EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. Herrstedt describes that the above steps in the dosing regimen are effective to treat both nausea and vomiting during a 5-day period. *Id.*, 146. Further, Herrstedt describes the above steps are effective for treating both nausea and vomiting to a greater extent during the 5-day period as compared to a

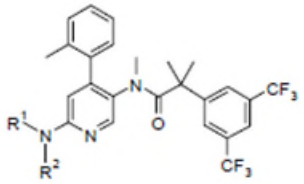
drug combination of just the 5-HT_3 receptor antagonist and dexamethasone. *Id.*, 146-147. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

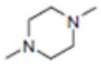
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*, 17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1

receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in Herrstedt.

826. Hargreaves explains NK_1 receptor occupancy of greater than 75% is associated with therapeutic effectiveness. EX1012 (Hargreaves), Abstract, 23, Fig. 6B. Hargreaves also teaches to measure NK_1 receptor occupancy in the striatum. As I explain further below, a POSA would have understood the therapeutically effective dose of netupitant would likely occupy at least 75% of NK_1 receptors in the striatum after prophylactic administration. Section XXII.A; *see also* Sections V.C-V.D, above. The skilled artisan would have reasonably expected that a prophylactically administered therapeutically effective dose of netupitant (e.g., 300 mg) would naturally result in very high occupancy of NK_1 receptors in the striatum (e.g., greater than 70%) and that due to netupitant's long half-life, it is a natural result that there would still be high occupancy of the striatum NK_1 receptors at 72 hours.

827. The sections below explain in more detail how Herrstedt, Bös, and Hargreaves disclose each and every element of claims 7, 16, and 22.

A. Claims 7, 16, 22

> **7.** The method of claim 1, wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors seventy-two hours after said administration.

> **16**. The method of claim 2, wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors seventy-two hours after said administration.
>
> **22**. The method of claim 3, wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors seventy-two hours after said administration.

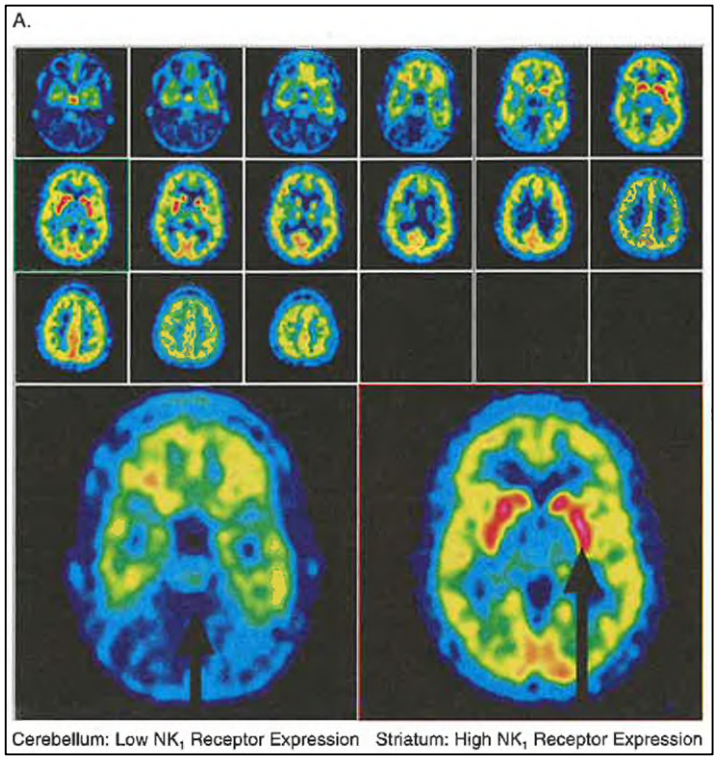
828. Claims 7, 16, and 22 each depends from independent claims 1, 2, and 3 (respectively) and additionally recites said netupitant occupies at least 70% of said patient's striatum NK_1 receptors seventy-two hours after said administration.

829. As I previously addressed above, each of claims 1, 2, and 3 was obvious over the combination of Herrstedt and Bös. *See* Sections XX.A-XX.C, above. It is my opinion that the combination of Herrstedt, Bös, and Hargreaves teaches or suggests claims 7, 16, and 22.

830. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of NK_1 receptor antagonists that are administered, e.g. orally, for treatment of emesis. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the

striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

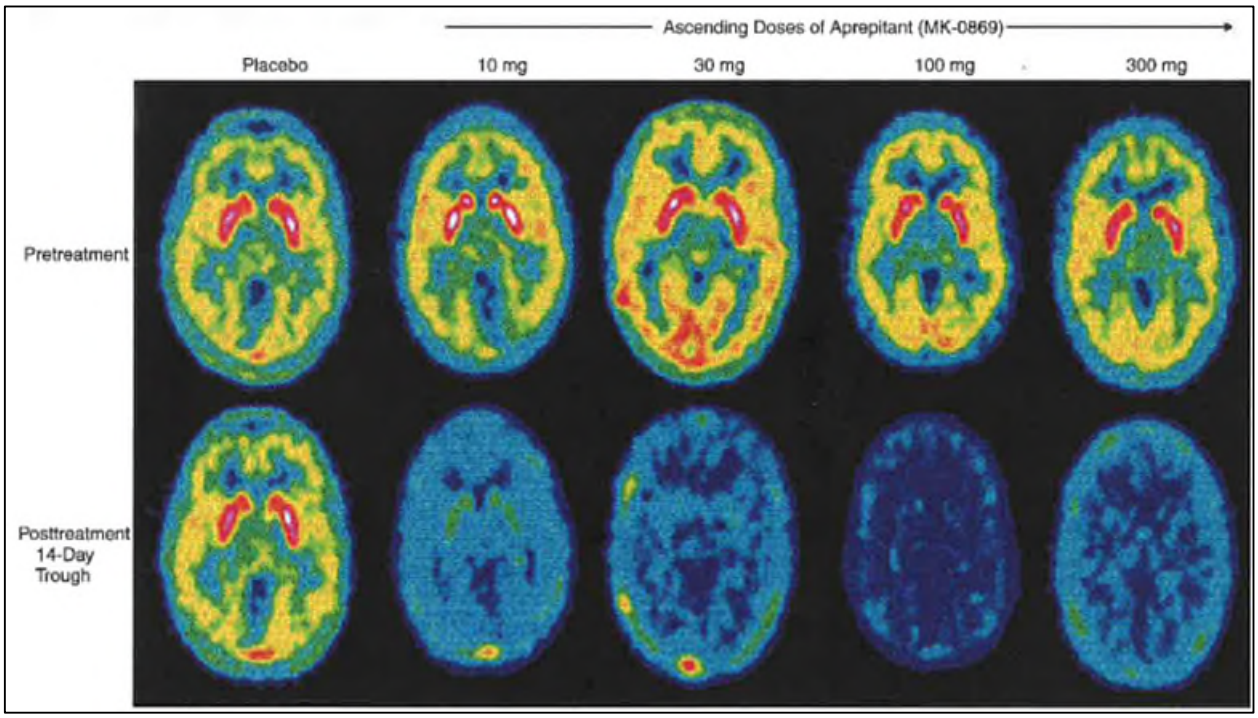
831. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

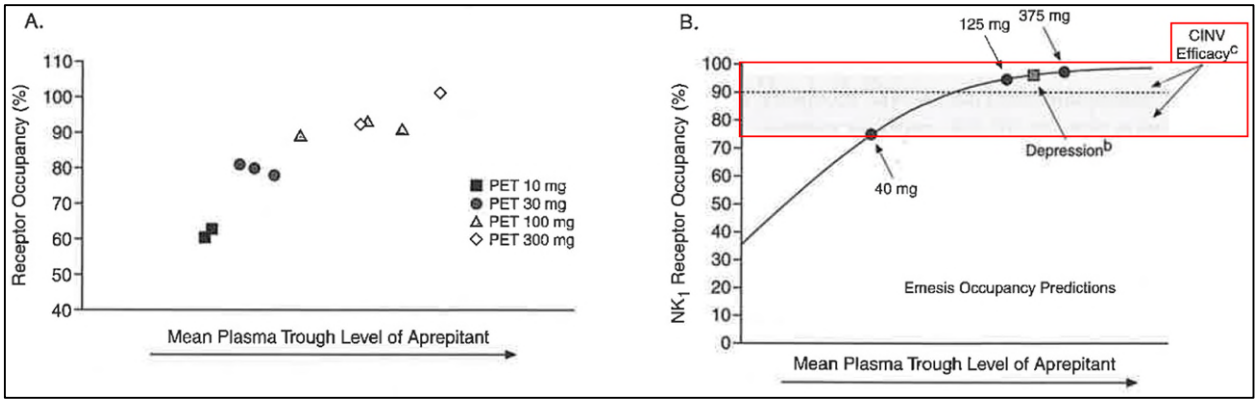
EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).



832. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS (Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös, and Hargreaves teaches or suggests a therapeutically effective amount providing blood levels wherein netupitant occupies at least 70% of the patient's striatum NK_1 receptors. Furthermore, it would have been obvious to a POSA that administering the therapeutically effective dose of netupitant would also occupy at least 75% (i.e., at least 70%) of neurokinin-1 (NK_1) receptors in the striatum seventy-two hours after administration.

833. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent

feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Section V.D, above. Seventy-two hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Section V.D, above. The '297 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration." EX1004 ('297 patent), 4:28-43. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

834. Accordingly, it is my opinion that each of claims 7, 16, and 22 as a whole was obvious over the combination of Herrstedt, Bös, and Hargreaves.

B. Motivation to Combine

835. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to treat nausea and vomiting in a patient during the acute and delayed phases of CINV in response to highly emetogenic chemotherapy with the triple antiemetic combination therapy provided in Herrstedt, using therapeutically effective amounts of the new NK_1 and 5-HT_3 receptor antagonists as claimed. *See* Sections XX.A-XX.C, XX.H above. I

described that persons having ordinary skill in the art would have had good reason to prophylactically treat (on Day 1, prior to chemotherapy) patients receiving highly emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt triple therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 and NK_1 receptor antagonists administered with dexamethasone on Day 1 (prior to chemotherapy) provided antiemetic effect). Additionally, I explained that a person having ordinary skill in the art would have modified the Herrstedt triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron.

836. The person having ordinary skill in the art also would have modified the Herrstedt triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Sections XX.A-

XX.C, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös explained the netupitant is administered orally (administration of oral doses as compared to intravenous has benefits as I described above) (*id.*, 19:2-38) and provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

837. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

838. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases, and to evaluate the effect using PET imaging as described in Hargreaves.

C. Reasonable Expectation of Success

839. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt triple active combination therapy with the claimed netupitant and palonosetron therapeutics. *See* Sections XX.A-XX.C, XX.I, above. I explained, for example, that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome.

840. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome.

Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant.

841. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XXII.A, above. The POSA would have understood that such studies were routinely conducted, and because the receptor occupancy being evaluated would be the same (NK_1 receptors in the striatum), it would have been routine to evaluate the effect of netupitant in the same manner described in Hargreaves.

842. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and Hargreaves to arrive at the claimed invention, and the POSA would have had a

reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXIII. ['357 PATENT GROUND 1] '357 PATENT CLAIMS 1-17, 40, 52-54, AND 56-62 WERE OBVIOUS OVER HERRSTEDT AND BÖS

843. For the reasons discussed in detail below, it is my opinion that each of claims 1-17, 40, 52-54, and 56-62 of the '357 patent was obvious as a whole. The obviousness of claims 1-17, 40, 52-54, and 56-62 is exemplified by disclosures in the Herrstedt and Bös references.

844. I have evaluated below whether the combination of Herrstedt and Bös discloses each and every element of each of claims 1-17, 40, 52-54, and 56-62 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

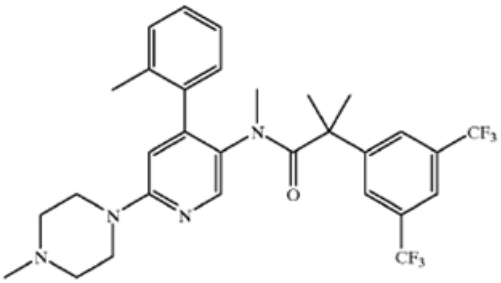
845. As a high-level summary, Herrstedt discloses methods of treating both chemotherapy induced nausea and vomiting (CINV). EX1010 (Herrstedt), 143, 146. Herrstedt discloses administering to the subject receiving chemotherapy on day one a therapeutically effective amount of a 5-HT_3 receptor antagonist (EX1010 (Herrstedt), 146) and teaches that palonosetron is a new 5-HT_3 receptor antagonist (*Id.*). Herrstedt also describes administering to the subject receiving chemotherapy

an NK_1 receptor antagonist (aprepitant) in a therapeutically effective amount. EX1010 (Herrstedt), 146. Herrstedt also discloses administering to the subject receiving chemotherapy dexamethasone. EX1010 (Herrstedt), 146-147. Herrstedt explains the dexamethasone is administered in a lower dose than what would typically be given but was effective when administered as discussed in Herrstedt's combination therapy (i.e., a sub-therapeutic dose). EX1010 (Herrstedt), 146-147. Because Herrstedt describes dexamethasone has twice the AUC concentration in the combination therapy, it teaches a POSA to decrease the first dose of dexamethasone by about 50% compared to the standard 20 mg day one dose. EX1010 (Herrstedt), 147. By achieving the desired therapeutic effect of treating CINV, Herrstedt teaches administration of its triple therapy combination induces in the subjects receiving chemotherapy blood levels of the 5-HT_3 receptor antagonist (palonosetron) and the NK_1 receptor antagonist (aprepitant) effective to treat the CINV. *Id.*, 146-147. Bös describes its "Formula Ib" as a new NK_1 receptor antagonist. Bös explains:

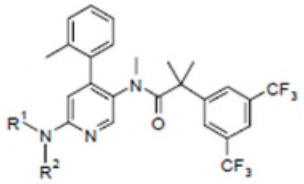
> The compound of formula Ib and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

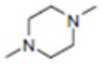
EX1014 (Bös), 14:31-38. The affinity of formula Ib for human NK_1 receptors was evaluated and formula Ib was shown to be "a potent and selective antagonist." *Id.*, 17:61-18:48; *see also id.*, 18:60-63 ("a competitive antagonist at human

recombinant NK_1 receptors"); *id.*, 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). A POSA would have known Bös formula Ib was netupitant.



Formula Ib
EX1014 (Bös), 14:9-30.



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5

Netupitant
EX1011 (Hoffmann), Table 4.

For ease of reference, below I refer to Bös' formula Ib as netupitant. It is my opinion that it would have been obvious to a POSA to employ Bös' second generation NK_1 receptor antagonist, netupitant, in place of the existing NK_1 receptor antagonist (aprepitant) in the triple-agent combination treatment disclosed in Herrstedt.

846. The sections below explain in more detail how Herrstedt and Bös disclose each and every element of claims 1-17, 40, 52-54, and 56-62. I first analyze independent claims 1, 2, and 4 of the challenged '357 patent. Thereafter, I analyze dependent claims 3, 5-17, 40, 52-54, and 56-62.

A. Claim 1

1[pre]. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising

847. I have reproduced above the preamble of claim 1 of the '357 patent. Herrstedt teaches a "method of treating chemotherapy induced nausea and vomiting (CINV)" as disclosed in the preamble of claim 1. For example, Herrstedt teaches methods for prophylactically treating "***[c]hemotherapy-induced nausea and vomiting***" in a patient. EX1010 (Herrstedt), 143. Herrstedt pronounces that, with its disclosure, "evidence-based guidelines for the ***treatment of chemotherapy-induced nausea and vomiting*** will be given." *Id.*, Abstract. Herrstedt explains its triple therapy combination builds on antiemetic combinations that "have significantly improved the prophylaxis of chemotherapy-induced emesis." *Id.*

848. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 1.

1(a). administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

849. I have reproduced above the administering step (a) element of claim 1. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the administering step of claim 1(a).

850. Herrstedt expressly discloses multiple studies administering to subjects receiving chemotherapy a triple-drug regimen including a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone. EX1010 (Herrstedt), 146. Herrstedt explains that a therapeutically effective amount of the 5-HT_3 receptor antagonist is administered to subjects receiving chemotherapy both in the

standard study (two agent combination: 5-HT_3 receptor antagonist and dexamethasone) and in the study evaluating the triple therapy adding NK_1 receptor antagonist:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline…. Two of the HEC studies used an identical design comparing ***ondansetron*** [5-HT_3 receptor antagonist], ***dexamethasone*** and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ***ondansetron*** [5-HT_3 receptor antagonist], ***dexamethasone*** and ***aprepitant*** [NK_1 receptor antagonist] day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3.

EX1010 (Herrstedt), 146 (citations omitted). Herrstedt teaches the triple-agent regimen (5-HT_3 receptor antagonist, NK_1 receptor antagonist, and dexamethasone) provided "a statistical[] benefit favouring" the triple agent combination across multiple studies. *Id*; *see also id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("[A] complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm."). Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. Poli-Bigelli and Hesketh both expressly confirm Herrstedt's summary of administering to subjects receiving chemotherapy a triple-

drug regimen including a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone. EX1039 (Poli-Bigelli), Abstract ("Patients with cancer who were scheduled to receive treatment with high-dose cisplatin chemotherapy were randomized…. The aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg."); EX1037 (Hesketh), Abstract ("Patients receiving cisplatin ≥ 70 mg/m^2 for the first time were given…an aprepitant regimen (aprepitant plus ondansetron and dexamethasone on day 1.")).

851. Herrstedt teaches or suggests administering to a subject receiving chemotherapy a triple-agent regimen including palonosetron. For example, Herrstedt identifies palonosetron as a favorable 5-HT_3 receptor antagonist for treating emesis. EX1010 (Herrstedt), 146. Herrstedt specifically teaches palonosetron differed from other 5-HT_3 receptor antagonists because it showed beneficial properties "in the treatment of delayed emesis from MEC" and also had an order of magnitude increase in half-life as compared to the 5-HT_3 receptor antagonist ondansetron. *Id.*, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours); *see also id.*, 146 ("in the MEC studies some of the evaluable parameters ***significantly favoured palonosetron***."). Herrstedt further describes palonosetron as a suitable substitution for ondansetron for treating emesis, stating: "Palonosetron has been compared to ondansetron and dolasetron in

three randomized, double-blind trials" and each "demonstrated that palonosetron was not inferior to dolasetron and ondansetron." *Id.*, 146. Thus, a POSA would have had good reason to employ a therapeutically effective amount of the "significantly favoured" palonosetron as the 5-HT_3 receptor antagonist to said subject receiving chemotherapy. Furthermore, the POSA would have had a reasonable expectation of success in making such a substitution because both palonosetron and ondansetron worked through an identical mechanism (i.e., 5-HT_3 receptor antagonism) to achieve the same therapeutic result (i.e., anti-emesis).

852. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil

and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis). Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a therapeutically effective dose.

853. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable

in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18. Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation

NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

854. Accordingly, Herrstedt discloses administering to a subject receiving chemotherapy a regimen of a 5-HT_3 receptor antagonist, an NK_1 receptor antagonist, and dexamethasone, Herrstedt discloses palonosetron as a favorable alternative 5-HT_3 receptor antagonist to be employed in its triple therapeutic regimen, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a POSA had good reasons to use a therapeutically effective amount of palonosetron, netupitant, and dexamethasone for treatment of CINV, such as in the method disclosed in Herrstedt.

855. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in claim element 1(a).

856. The combination of Herrstedt and Bös thus teaches all of the elements of claim 1 and rendered the claim obvious as a whole.

B. Claim 2

2[pre]. A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising

857. I have reproduced above the preamble of claim 2 of the ’357 patent. Herrstedt teaches a “method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy” as disclosed in the preamble of claim 2. For example, Herrstedt teaches methods for prophylactically treating “***[c]hemotherapy-induced nausea and vomiting***” in patients receiving chemotherapy. EX1010 (Herrstedt), 143. Herrstedt pronounces that, with its disclosure, “evidence-based guidelines for the ***treatment of chemotherapy-induced nausea and vomiting*** will be given.” *Id.*, Abstract. Herrstedt explains its triple therapy combination builds on antiemetic combinations that “have significantly improved the prophylaxis of chemotherapy-induced emesis.” *Id.* Herrstedt describes the triple therapy combination is useful for preventing nausea and vomiting in subjects receiving chemotherapy including cisplatin. *Id.*, 146.

858. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 2.

2(a). administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.

859. I have reproduced above the administering step (a) element of claim 2. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the administering step of claim 2(a).

860. Herrstedt expressly discloses multiple studies administering to subjects receiving chemotherapy a triple-drug regimen including an NK_1 receptor antagonist and dexamethasone. EX1010 (Herrstedt), 146. Herrstedt describes:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline…. Two of the HEC studies used an identical design comparing ondansetron [5-HT_3 receptor antagonist], ***dexamethasone*** and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron [5-HT_3 receptor antagonist], ***dexamethasone*** and ***aprepitant*** [NK_1 receptor antagonist] day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3.

EX1010 (Herrstedt), 146 (citations omitted). Herrstedt teaches the triple-agent regimen (including NK_1 receptor antagonist and dexamethasone) provided "a statistical[] benefit favouring" the triple agent combination across multiple studies. *Id*; *see also id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("[A] complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm."). Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. Poli-Bigelli and Hesketh both expressly confirm Herrstedt's summary administering to subjects receiving chemotherapy a triple-drug regimen

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861. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of an effective amount of netupitant for treating emesis. For example, in Bös:

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in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

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NK_1 receptor antagonist (aprepitant) in Herrstedt's antiemetic therapy combination. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism).

863. Before looking to evaluate whether the prior art discloses "a sub-therapeutic dose of dexamethasone," I look to the specification of the '357 patent exclusively to understand what the claim means when it says a "sub-therapeutic dose" of dexamethasone. The '357 patent defines sub-therapeutic doses as those that would be ineffective if administered by itself. EX1002 ('357 patent), 5:13-17 ("***sub-therapeutic*** doses (i.e., ***doses at which the dexamethasone would be ineffective if administered by itself***)."). Additionally, the specification admits that doses of dexamethasone smaller than 20 mg (for day one administration) or 16 mg (for subsequent day administration) would be ineffective if administered by itself. The '357 patent describes a 20 mg (day one) dose or 16 mg (days two through four) dose of dexamethasone was known in the field as the minimum therapeutically effective dose for treating CINV:

> The ***minimum effective dose of dexamethasone***, when used to treat CINV induced by highly emetogenic chemotherapy, has been demonstrated to be ***20 mg***. administered orally or by injection ***on day***

> ***one, and sixteen mg***. administered orally or by injection ***on days two, three and four***. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the ***minimum effective dose of dexamethasone*** is ***20 mg***. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1002 ('357 patent), 7:62-8:4 (citing EX1019 (Jordan), published in 2007 and more than one year prior to the critical date). As defined in the patent specification, the claim term "a sub-therapeutic dose of dexamethasone" encompasses any day one dose of less than 20 mg and any day two through four dose of less than 16 mg. The prior art routinely described this same 20 mg dose as the standard day one dose for treating emetogenic chemotherapy. *See, e.g.*, EX1010 (Herrstedt), 145 ("single intravenous dose of 20 mg" for highly emetogenic chemotherapy); EX1025 (Chawla), 2292 (standard therapy combination included oral dexamethasone 20 mg on Day 1); EX1013 (MASCC), Table 3 (20 mg dexamethasone for patients not receiving aprepitant).

864. Understanding the claim term as illustrated in the patent specification, Herrstedt discloses administering to a subject receiving chemotherapy a regimen including a sub-therapeutic dose of dexamethasone. For example, Herrstedt teaches administering to subjects a sub-20 mg day one dose of dexamethasone for the treatment of moderately emetogenic chemotherapy, a treatment that leads to CINV.

EX1010 (Herrstedt), 145-147. In contrast to the standard 20 mg day one dose, Herrstedt teaches that the day one dexamethasone should be administered in a reduced amount—about 25% to 50% less than the 20 mg (minimally effective) standard dose discussed above. *Id.* Poli-Bigelli and Hesketh further confirm that Herrstedt's triple agent regimen includes a sub-therapeutic dose of dexamethasone. In Poli-Bigelli, "[t]he aprepitant group received oral aprepitant 125 mg, intravenous ondansetron, and oral ***dexamethasone 12 mg on Day 1;*** oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on Days 2-***3; and oral ***dexamethasone 8 mg on Day 4***." EX1039 (Poli-Bigelli), Abstract. Similarly, in Hesketh, "Patients in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral ***dexamethasone 12 mg on day 1***, oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on days 2 and 3***, and oral ***dexamethasone 8 mg on day 4***." EX1037 (Hesketh). As noted above, the '357 patent specification defines "a sub-therapeutic dose of dexamethasone" encompasses any day one dose of less than 20 mg and any day two through four dose of less than 16 mg. Thus, each of Poli-Bigelli and Hesketh's dexamethasone administrations above satisfy administering to subjects receiving chemotherapy a regimen including a sub-therapeutic dose of dexamethasone.

865. Herrstedt explains that due to metabolic interactions of corticosteroids (e.g., dexamethasone or methylprednisolone) and the NK_1 receptor antagonist

(aprepitant), the corticosteroid should be administered in a lower-than-typically-therapeutic dose when treatment includes the NK_1 receptor antagonist. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced*** by 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

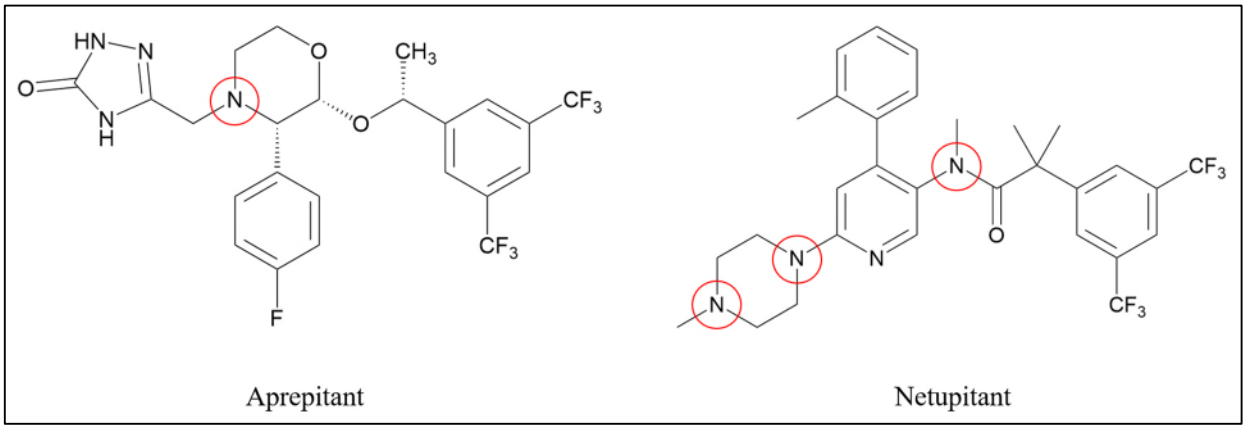
EX1010 (Herrstedt), 147. Herrstedt further explains that:

> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Therefore Herrstedt suggests the dose of dexamethasone—when administered with NK_1 receptor antagonist—should be a sub-therapeutic dose which, by itself would be ineffective against CINV, but when administered in combination with NK_1 receptor antagonist is effective against CINV because it provides the same total exposure of dexamethasone AUC. Thus, Herrstedt describes administering to the subject receiving chemotherapy a regimen that includes a sub-therapeutic dose of dexamethasone.

866. Based on the experience with aprepitant, a POSA would have had good reason to determine the dexamethasone AUC when administered with netupitant compared to administration of dexamethasone alone. Evaluating such drug-drug interactions was well-known and routine in the field. EX1049 (Zhou), 318 ("Drug-drug interactions remain an important issue in clinical practice and drug development"). Evaluating such drug-drug interactions (e.g., NK_1-receptor-antagonist-induced dexamethasone potentiation) was a fundamental prerequisite when administering a combination therapy, such as the combination antiemetic therapy at issue. EX1010 (Herrstedt), 147 ("Risk of drug-drug interactions with the use of anti-emetics" due to "concomitant treatment with supportive care drugs" should be evaluated). Understanding the interaction of therapeutic agents with their metabolism provided necessary insight for evaluating drug-drug interactions. EX1044 (Schoenwald), 86 ("By understanding which metabolic steps may be susceptible to induction or inhibition by other drugs, specific *in vitro* or clinical drug interaction studies may be conducted to determine the potential risks of drug-drug interactions."). Among other interactions, a POSA would have had good reason to measure the impact of netupitant administration on the cytochrome P450 (CYP) 3A4 ("CYP3A4") enzyme-mediated metabolism of dexamethasone. This particular cytochrome P450 was known to "metaboliz[e] more than 50% of [] clinically used drugs." EX1049 (Zhou), 310. In addition to metabolizing "more

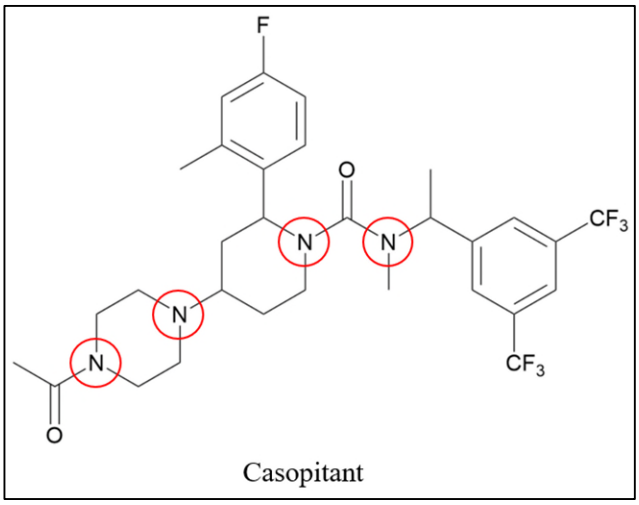
than 50% [of] therapeutic drugs" CYP3A4 was known to have "very broad" substrate specificity "with an extremely large number of structurally divergent chemicals being metabolized." *Id.*, 311. In other words, it was well-known CYP3A4 had high "ligand promiscuity" for metabolism and a high likelihood of being involved in the metabolism of a given therapeutic agent. *Id.* Additionally, CYP3A4 was known to be inhibited by a variety of substrates sharing common structural features with aprepitant and netupitant. For example, drugs known to inactivate CYP3A4 "often possess a number of structural similarities such as a tertiary amine function[.]" EX1049 (Zhou), 314. Both aprepitant and netupitant had such tertiary amine function, as shown in the below figure (red circles annotating tertiary amines).



Aprepitant Netupitant

It was known that aprepitant was a substrate and moderate inhibitor of CYP3A4, leading to increased AUC exposure of dexamethasone. EX1010 (Herrstedt), 147 (50% increase of dexamethasone AUC). Likewise, it was known that the NK_1 receptor antagonist casopitant—structurally similar to netupitant—was also a

substrate and weak-to-moderate inhibitor of CYP3A4, requiring "a reduction in dexamethasone dose of 40-50%, when repeat-dose oral dexamethasone is to be co-administered with oral casopitant." EX1042 (Ruhlmann), 377-378; *see also* the below figure where I provide the structure with annotations of tertiary amines.



Casopitant

Thus, a POSA would have expected netupitant to similarly act as substrate and inhibitor of CYP3A4. Accordingly, it would have been obvious and routine to a POSA in view of Herrstedt and Bös to lower the dexamethasone dose accordingly. Because the patent defines the sub-therapeutic dose of dexamethasone to encompass any day one dose below the standard 20 mg dose and any day two through four dose below the standard 16 mg dose, any actual reduction from the standard doses satisfies the claims.

867. Having good reason to co-administer netupitant with dexamethasone (as discussed above), the reduced metabolism of dexamethasone when co-administered with netupitant is a property that necessarily and naturally flows from

the combination. Accordingly, a POSA performing routine metabolism studies on the combination therapy would reasonably expect to measure the increased dexamethasone AUC and to reduce the dexamethasone day one dose below the 20 mg (minimally effective) standard dose, as well as to reduce the dexamethasone days two through four doses below the 16 mg standard dose, which dose reduction the patent itself admits satisfies the claim.

868. Accordingly, it is my opinion that the combination of Herrstedt and Bös discloses the subject matter recited in claim element 2(a).

869. The combination of Herrstedt and Bös thus teaches all of the elements of claim 2 and rendered the claim obvious as a whole.

C. Claim 4

4[pre]. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising

870. I have reproduced above the preamble of claim 4 of the ’357 patent. Herrstedt teaches a “method of treating chemotherapy induced nausea and vomiting (CINV)” as disclosed in the preamble of claim 4. For example, Herrstedt teaches methods for prophylactically treating “***[c]hemotherapy-induced nausea and vomiting***” in a patient. EX1010 (Herrstedt), 143. Herrstedt pronounces that, with its disclosure, “evidence-based guidelines for the ***treatment of chemotherapy-induced nausea and vomiting*** will be given.” *Id.*, Abstract. Herrstedt explains its

triple therapy combination builds on antiemetic combinations that "have significantly improved the prophylaxis of chemotherapy-induced emesis." *Id.*

871. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in the preamble of claim 4.

> **4(a).** inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

872. I have reproduced above the inducing step (a) element of claim 4. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the administering step of claim 4(a).

873. I explained at length above why administering, to a subject receiving chemotherapy, a regimen including therapeutically effective amounts of palonosetron and netupitant in combination with dexamethasone was obvious in view of Herrstedt and Bös. *See* Section XXIII.A, above (claim element 1(a)). As I explain below, palonosetron and netupitant are delivered to the relevant receptors (e.g., 5-HT_3 and NK_1 receptors in the CNS) through the circulatory system. Essentially, when treating CINV in patients receiving chemotherapy, therapeutically effective levels of the antagonists are achieved in the blood, normally via intravenous or oral administration, causing therapeutically effective amounts of these antagonists to arrive at the target receptors in the CNS, thereby treating CINV. In the normal course, administering therapeutically effective amounts of palonosetron and netupitant to a subject receiving chemotherapy thus

operates by "inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV." Accordingly, the prior art teaches, suggest, or renders obvious this element for the same reasons discussed above that it teaches, suggests, or renders obvious administration of therapeutically effective amounts of palonosetron and netupitant.

874. Moreover, I observe that nowhere in the '357 patent specification is there any discussion of "blood levels" let alone any definition of what constitutes "blood levels…effective to treat said CINV." The '357 patent includes one example (Example 2) that measured pharmacokinetics of therapeutics using blood sampling but does not indicate what, if any, of the results disclose blood levels effective to treat CINV. EX1002 ('357 patent), 14:48-15:60. Indeed, '357 Example 2 is not concerned with therapeutic effectiveness but rather with confirming that "palonosetron shows a better pharmacokinetic profile when combined with Netupitant as opposed to administered as a single dose of palonosetron." *Id.*, 15:41-47.

875. The prosecution history confirms that the claimed "blood levels" of a drug "effective to treat said CINV" is equivalent to a therapeutically effective amount of the drug. During prosecution of the application that issued as the '357 patent, the patent applicant provided to the USPTO a table showing where the specification supported certain claim limitations. EX1006 (file history of '927

application), 293-294. In that table, the applicant indicated that "***netupitant blood levels effective to treat CINV*** during acute and delayed phase" and "***palonosetron blood levels effective to treat CINV*** during acute phase" were solely supported by "Table 5" of the specification. *Id.*, 294. I reproduce below Table 5 from that specification:

TABLE 5: COMPLETE RESPONSE RATE FOR THE OVERALL, ACUTE AND DELAYED PHASE: MFAS Population

Efficacy endpoint	Palo alone (n=136)	Palo + Netu 100 mg (n=135)	Palo + Netu 200 mg (n=137)	Palo + Netu 300 mg (n=135)	Aprepitant Regimen (N=134)
CR, Overall Phase, 0-120h					
Percent of Patients	76.5	87.4	87.6	89.6	86.6
Difference from Palo alone (%)		10.9	11.1	13.2	10.1
p-value (*)		0.018	0.017	0.004	0.027
CR, Acute Phase, -24h					
Percent of Patients	89.7	93.3	92.7	98.5	94.8
Difference from Palo alone (%)		3.6	3.0	8.8	5.1
p-value (*)		0.278	0.383	0.007	0.114
CR, Delayed Phase, 25-120h					
Percent of Patients	80.1	90.4	91.2	90.4	88.8
Difference from Palo alone (%)		10.2	11.1	10.2	8.7
p-value (*)		0.018	0.010	0.018	0.043

(*) p-value from logistic regression analysis, aprepitant p-value from post-hoc logistic regression analysis.

EX1006 (file history of '927 application), 127; *see also* EX1002 ('357 patent), Table 5 (same). This table does not disclose any measurement of blood levels and instead attributes efficacy to therapeutically effective doses of netupitant and palonosetron. Thus, patent applicant itself treated therapeutically effective blood levels of a drug as equivalent to administering a therapeutically effective amount of said drug.

876. Related prosecution history further suggests the claimed "blood levels…effective to treat said CINV" is equivalent to a therapeutically effective

amount. During prosecution of the application that issued as the ’297 patent, I understand the examiner treated the recited blood level as equivalent to “***effective amounts*** of each component to prevent acute and delayed emesis in patients receiving highly emetogenic cancer chemotherapy[.]” EX1008 (file history of ’050 application), 120; *see also id.*, 166-167. I also understand that the patent applicant did not rebut the examiner’s understanding, but instead argued there was (i) unexpected results from the combination of palonosetron and netupitant; (ii) no reasonable likelihood of predicting the dose of netupitant; and (iii) no reasonable expectation netupitant would be independently effective. EX1008 (file history of ’050 application), 152-156. Thus, it is my understanding that the patent applicant agrees the claim term “blood levels” of a drug “effective to treat said CINV” is equivalent to a “therapeutically effective amount” of said drug.

877. Additionally, “inducing” the effective blood levels is equivalent to administering the therapeutically effective amount in any manner that operates via the blood, which includes oral and intravenous administration (both methods known in the prior art). This is confirmed both by the specification itself and arguments made by patent owner. The ’357 patent explains that “inducing plasma levels” of a therapeutic agent (e.g., netupitant, palonosetron) corresponds to administration of the therapeutic agent. EX1002 (’357 patent), 10:22-29 (“netupitant can be ***administered*** in prodrug form, in which case the invention will

provide a method of treatment by ***inducing plasma levels of netupitant***"); *id.* ("the plasma level of netupitant ***induced*** by the prodrug administration will ***correspond to the level attained by the administration*** of netupitant…in the doses and routes of administration described herein."). Additionally, when applying for "Patent Term Extension" for the '357 patent, I understand that Helsinn argued that ***administration*** of a prodrug form of netupitant corresponded with ***inducing*** the netupitant plasma levels. EX1006 (file history of '927 application), 461.

878. Thus, in sum, a person of ordinary skill in the art would have understood that "administering, in a subject receiving chemotherapy, therapeutically effective amounts of palonosetron and netupitant in a combination regimen" naturally satisfies the claimed "inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV" whenever the palonosetron and netupitant are delivered through the blood (i.e., when administration is accomplished orally or intravenously).

879. Herrstedt expressly discloses multiple studies treating CINV by administering to subjects receiving chemotherapy therapeutically effective amounts of a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist in a combination regimen with dexamethasone. Herrstedt summarizes multiple studies for antiemetic treatment of patients receiving highly emetogenic chemotherapy, wherein the antiemetic treatment is a triple-drug combination comprising (i) a 5-

HT_3 receptor antagonist (ondansetron), (ii) an NK_1 receptor antagonist (aprepitant), and (iii) dexamethasone. EX1010 (Herrstedt), 146 ("Two of the ***HEC*** studies used an identical design…***ondansetron***, ***dexamethasone*** and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes benefits to patients receiving the triple-drug antiemetic combination. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.").

880. Herrstedt teaches or suggests administering palonosetron as its 5-HT_3 receptor antagonist. Herrstedt identifies palonosetron as a favorable 5-HT_3 receptor antagonist for treating emesis. EX1010 (Herrstedt), 146. Herrstedt specifically teaches palonosetron differed from other 5-HT_3 receptor antagonists because it showed beneficial properties "in the treatment of delayed emesis from MEC" and also had an order of magnitude increase in half-life as compared to the 5-HT_3 receptor antagonist ondansetron. *Id.*, 146, Table 3 (palonosetron half-life 38-40 hours; ondansetron half-life 4-6 hours); *see also id.*, 146 ("in the MEC studies some of the evaluable parameters ***significantly favoured palonosetron***."). Herrstedt further describes palonosetron as a suitable substitution for ondansetron

for treating emesis, stating: "Palonosetron has been compared to ondansetron and dolasetron in three randomized, double-blind trials" and each "demonstrated that palonosetron was not inferior to dolasetron and ondansetron." *Id.*, 146. Thus, a POSA would have had good reason to employ a therapeutically effective amount of the "significantly favoured" palonosetron as the 5-HT_3 receptor antagonist to said patient. Furthermore, the POSA would have had a reasonable expectation of success in making such a substitution because both palonosetron and ondansetron worked through an identical mechanism (i.e., 5-HT_3 receptor antagonism) to achieve the same therapeutic result (i.e., anti-emesis).

881. Though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists. EX1010 (Herrstedt), Abstract. Bös not only discloses netupitant ("formula Ib") as a potent and selective NK_1 receptor antagonist, but also recommends use of a therapeutically effective amount of netupitant for treating emesis. For example, in Bös:

> The compound of formula Ib [netupitant] and its salts is also characterized by ***valuable therapeutic properties*** as a ***highly selective*** antagonist of the Neurokinin 1 (NK-1, substance P)[.]

EX1014 (Bös), 14:31-38; *see also id.*, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil

and blocks emesis in ferrets and [S]ancus murinus with similar potency."). Bös describes that:

> [T]he most preferred indications in accordance with the present invention are those which include ***disorders of the central nervous system***, for example indications for the treatment or prevention of certain depressive disorders, anxiety or ***emesis by the administration of NK-1 receptor antagonists***.

Id., 4:15-24. Bös explains that "pharmacological activity of the compounds of this invention as NK-1 receptor antagonists" have activity that "is correlated with treatment of" disorders related to the central nervous system (CNS). *Id.*, 42-48. Bös teaches that selective NK_1 receptor antagonists are "particularly useful for treating CNS disorders, such as depression, anxiety or emesis." *Id.*, 9:22-29; *see also id.*, 19:10-30 (netupitant effective for treatment of emesis).

882. Bös teaches a therapeutically effective amount of its NK_1 receptor antagonists (including netupitant) for a patient to be within the range of about 10 mg to 1,000 mg. Bös states:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention*** should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. Thus, Bös discloses netupitant as a potent and selective NK_1 receptor antagonist and teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective dose.

883. It is my opinion that a POSA would have understood Bös as providing good reason to replace Herrstedt's NK_1 receptor antagonist (aprepitant) with the second generation NK_1 receptor antagonist of Bös (netupitant). For example, A POSA would have understood that excellent CNS penetration was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. The prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

> The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS), where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative. High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex. A role for SP in the

> regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients. Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.

EX1012 (Hargreaves), 18; *see id.*, 18 (SP-NK_1 receptor system known to have neuro-anatomical overlap with 5-HT family of receptors). Therefore a POSA would have been motivated to substitute the new NK_1 receptor antagonist (netupitant), for the first generation NK_1 receptor antagonist (aprepitant) in Herrstedt's combination regimen with palonosetron and dexamethasone. Further, it is my opinion that a POSA would have had a high likelihood of succeeding in substituting netupitant for aprepitant in the Herrstedt combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (treating CINV) through the very same mechanism (NK_1 receptor antagonism).

884. Accordingly, Herrstedt discloses administering to said subject a therapeutically effective amount of a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist in a combination regimen with dexamethasone, Herrstedt suggests employing palonosetron as its 5-HT_3 receptor antagonist, Bös discloses netupitant as a favorable alternative NK_1 receptor antagonist to aprepitant, and a

POSA had good reasons to use therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone for treatment of CINV in a subject receiving cancer chemotherapy, such as in the method disclosed in Herrstedt.

885. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in claim element 4(a).

886. The combination of Herrstedt and Bös thus teaches all of the elements of claim 4 and rendered the claim obvious as a whole.

D. Claim 3

> **3.** The method of claim 2, wherein the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

887. Claim 3 depends from independent claim 2 and additionally recites the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

888. As I previously addressed above, claim 2 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.B, above.

889. As I explained above for element 2(a), Herrstedt explains the day one dose of dexamethasone should be administered in a reduced amount—including by about 50 to 70%—compared to the minimum effective dose when administered alone (20 mg). As I explained above, it was known NK_1 receptor antagonists

doubled the AUC concentration of dexamethasone, and Herrstedt teaches reducing the dexamethasone dose in a corresponding amount. Herrstedt explains:

> Dexamethasone and methylprednisolone are sensitive to substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a ***two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism***. When methylprednisolone is given in combination with aprepitant the intravenous dose can be ***reduced by*** 25% and ***the oral dose by 50%*** to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant.

EX1010 (Herrstedt), 147. Herrstedt further explains that:

> During the development of aprepitant, ***it became clear that the dose of oral*** (and to a minor degree intravenous) ***corticosteroids had to be reduced*** due to interaction at the cytochrome P450 (CYP) 3A4 enzyme system between corticosteroids and aprepitant.

Id., 146. Herrstedt thus teaches reducing the dose of dexamethasone, when administered with an NK_1 receptor antagonist, by about 50% of the minimum effective dose when administered alone to achieve the same effective AUC concentration. Accordingly, Herrstedt discloses the limitation of claim 3. *See also* Sections IX.A, IX.E above (prior art taught to reduce dexamethasone when administered with NK_1 receptor antagonists).

890. Additionally, as I explained above, the ’357 patent admits the minimum effective dose of dexamethasone when administered alone against CINV

is 20 mg (for day one administration) or 16 mg (for subsequent day administration). The ’357 patent describes a 20 mg (day one) dose or 16 mg (days two through four) dose of dexamethasone was known in the field as the minimum therapeutically effective dose for treating CINV:

> The ***minimum effective dose of dexamethasone***, when used ***to treat CINV*** induced by highly emetogenic chemotherapy, has been demonstrated to be ***20 mg***. administered orally or by ***injection on day one, and sixteen mg***. administered orally or by injection ***on days two, three and four***. Jordan et al., THE ONCOLOGIST, Vol. 12, No. 9, 1143-1150, September 2007. When used to treat CINV induced by moderately emetogenic chemotherapy, the ***minimum effective dose of dexamethasone*** is ***20 mg***. administered orally or by injection on day one, and zero mg. on days two, three and four.

EX1002 (’357 patent), 7:62-8:4 (citing EX1019 (Jordan)).

891. Herrstedt’s examples administer dexamethasone in a dose within the range of about 50 to 70% of the above-described minimum effective dose. Herrstedt discloses that the administration details are provided “in the Poli-Bigelli study” and in the Hesketh study. EX1010 (Herrstedt), 146. Poli-Bigelli and Hesketh each administer day one dexamethasone in a dose of 12 mg (i.e., 60% of 20 mg) and administer on each of days two, three, and four dexamethasone in a dose of 8 mg (i.e., 50% of 16 mg) to treat CINV induced by highly emetogenic chemotherapy. EX1039 (Poli-Bigelli), Abstract (“Patients with cancer who were

scheduled to receive ***treatment with high-dose cisplatin chemotherapy*** were randomized…. The aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral ***dexamethasone 12 mg*** on Day 1; oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on Days 2-3;*** and oral ***dexamethasone 8 mg on Day 4***."); EX1037 (Hesketh), Abstract ("***Patients receiving cisplatin*** $\geq$ 70 mg/m^2 for the first time were given…an aprepitant regimen (aprepitant plus ondansetron and ***dexamethasone*** on day 1.")); *id.*, 4113 ("Patients in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral ***dexamethasone 12 mg on day 1***, oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on days 2 and 3***, and oral ***dexamethasone 8 mg on day 4***.").

892. Thus, Herrstedt discloses the sub-therapeutic dose of dexamethasone comprises from about 50 to 70% of a minimum effective dose when administered alone against CINV.

893. The combination of Herrstedt and Bös thus teaches all of the elements of claim 3 and rendered the claim obvious as a whole.

E. Claim 5

5. The method of claim 1, wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy.

894. Claim 5 depends from independent claim 1 and additionally recites the chemotherapy comprises moderately or highly emetogenic chemotherapy.

895. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.A, above.

896. Herrstedt discloses wherein the chemotherapy comprises moderately or highly emetogenic chemotherapy. As detailed above, Herrstedt discloses its antiemetic drug combination is administered for treatment of chemotherapy induced nausea and vomiting (CINV). *See* Claim 1, above. Herrstedt also describes efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***." EX1010 (Herrstedt), Abstract. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of ***cyclophosphamide plus an anthracycline***. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt also includes a table of chemotherapies and classifies cisplatin as highly emetogenic. *Id.*, Table 1. Another of Herrstedt's tables categorizes the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic. *Id.*, Table 4. Thus, the studies described above in Herrstedt evaluating the antiemetic combination to treat CINV are used to treat nausea and vomiting induced by moderately or highly emetogenic chemotherapy. EX1010 (Herrstedt), 146, Abstract.

897. Accordingly, it is my opinion that claim 5 as a whole was also obvious over Herrstedt and Bös.

F. Claim 6

6. The method of claim 1, wherein said chemotherapy comprises carboplatin.

898. Claim 6 depends from independent claim 1 and additionally recites said chemotherapy comprises carboplatin.

899. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.A, above.

900. Herrstedt suggests treating CINV comprising administering to a subject receiving chemotherapy its triple antiemetic regimen wherein the chemotherapy comprises carboplatin. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including by moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***"). Carboplatin is a moderately emetogenic chemotherapy. *Id.*, Table 1.

901. Although Herrstedt provides detailed summaries for its combination therapy treating CINV where the chemotherapy is highly emetogenic (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating CINV response to cisplatin. Instead, Herrstedt identifies that the NK_1 receptor antagonist is more

broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a $serotonin_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy includes carboplatin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

It would have been within a POSA's skill and abilities to apply Herrstedt's combination therapy for treating a highly or moderately emetogenic chemotherapy, such as any of those listed in Table 1. Because the '357 patent does not provide details for implementing its administration for the claimed chemotherapy agent, this further confirms it was within the skills of the POSA to do so. Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is

administered to treat CINV for moderately emetic chemotherapy including, e.g., carboplatin.

902. The ’357 patent does not ascribe any particular or unexpected results associated with treating CINV where the chemotherapy is carboplatin. I have reviewed the ’357 patent and do not observe any particular benefits linked with treating CINV where the chemotherapy is carboplatin. The sole disclosure of carboplatin is in a list merely identifying a group of moderately emetogenic chemotherapies. EX1002 (’357 patent), 8:45-50. Therefore, based on my review of the ’357 patent, there is no particular or unexpected benefit ascribed using the claimed method treating CINV wherein the chemotherapy is carboplatin.

903. Accordingly, it is my opinion that claim 6 as a whole was also obvious over Herrstedt and Bös.

G. Claim 7

> **7.** The method of claim 1, wherein the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

904. Claim 7 depends from independent claim 1 and additionally recites the netupitant and palonosetron are administered no more than one hour prior to administration of the chemotherapy.

905. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.A, above.

906. Herrstedt discloses the NK_1 receptor antagonist and 5-HT_3 receptor antagonist are administered in conjunction with the chemotherapy. Herrstedt summarizes two studies administering the triple antiemetic drug combination described above. *See* Claim 1, above; EX1010 (Herrstedt), 146. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) and employing palonosetron as the 5-HT_3 receptor antagonist (disclosed in Herrstedt) was obvious. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

907. A POSA reviewing Herrstedt would have understood that the NK_1 and 5-HT_3 receptor antagonists are administered no more than one hour prior to administration of the chemotherapy. *See*, *e.g.*, EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist administered one hour prior to cisplatin; 5-HT_3 receptor antagonist administered thirty minutes prior to cisplatin); EX1037 (Hesketh), 4113 (same). Poli-Bigelli and Hesketh both expressly confirm that the NK_1 receptor antagonist and 5-HT_3 receptor antagonist are administered no more than one hour prior to administration of the chemotherapy. Poli-Bigelli describes, with regard to its timing:

> One hour prior to cisplatin, patients received either aprepitant or placebo. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing aprepitant one hour prior to administration of cisplatin (and in combination with the other drugs disclosed in the regimen) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> One hour before cisplatin, patients received either aprepitant or placebo. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer the NK_1 receptor antagonist and 5-HT_3 receptor antagonist no more than one hour prior to administration of the chemotherapy, and would have had a reasonable expectation of success that such dosing would provide relief from emesis. As I explained above, the POSA also would have had good reason to employ netupitant as the NK_1 receptor antagonist and palonosetron as the 5-HT_3 receptor antagonist, and would have had a reasonable expectation that employing them no more than one hour prior to administration of the chemotherapy would also provide the treatment of CINV (e.g., due to similar treatment profiles and mechanisms of action).

908. Accordingly, it is my opinion that claim 7 as a whole was also obvious over Herrstedt and Bös.

H. Claims 8, 11, 14

8. The method of claim 1, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

11. The method of claim 2, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

14. The method of claim 4, wherein when said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, cisplatin, cyclophosphamide≧1500 mg/m^2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

909. Each of claims 8, 11, and 14 depends from independent claims 1, 2, and 4, respectively, and additionally recites said chemotherapy is highly emetic chemotherapy, the chemotherapy is selected from the group consisting of carmustine, ***cisplatin***, cyclophosphamide≧1500 mg/m2, dacarbazine, dactinomycin, mechlorethamine, streptozotocin and combinations thereof.

910. As I previously addressed above, each of claims 1, 2, and 4 was obvious over the combination of Herrstedt and Bös. *See* Sections XXIII.A-XXIII.C, above.

911. Herrstedt suggests the chemotherapy is highly emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including highly

emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly*** or moderately ***emetogenic chemotherapy***").

912. Herrstedt also discloses its antiemetic drug combination is administered to treat CINV where the chemotherapy is, for example, ***cisplatin***. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

913. Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting from other chemotherapeutic agents. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such highly emetogenic chemotherapy includes

cisplatin, mechloretamine, streptozocin, dacarbazine, and cyclophosphamide > 1500 mg/m^2. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy is highly emetic chemotherapy, and where the chemotherapy is any one of cisplatin, mechloretamine, streptozocin, dacarbazine, and cyclophosphamide > 1500 mg/m^2, or a combination thereof.

914. Accordingly, it is my opinion that each of claims 8, 11, and 14 as a whole was also obvious over Herrstedt and Bös.

I. Claims 9, 12, 15

9. The method of claim 1, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

12. The method of claim 2, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

> **15.** The method of claim 4, wherein when said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

915. Each of claims 9, 12, and 15 depends from independent claims 1, 2, and 4, respectively, and additionally recites said chemotherapy is moderately emetic chemotherapy, the chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide < 1500 mg/m^2, cytarabine > 1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, oxaliplatin and combinations thereof.

916. As I previously addressed above, each of claims 1, 2, and 4 was obvious over the combination of Herrstedt and Bös. *See* Sections XXIII.A-XXIII.C, above.

917. Herrstedt suggests the chemotherapy comprises moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

918. Although Herrstedt provides detailed summaries for its combination therapy for preventing CINV where the chemotherapy comprises highly

emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to the highly emetogenic cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting from other chemotherapeutic agents. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy includes carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1000 mg/m^2 (which includes cytarabine>1 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

It would have been within a POSA's skill and abilities to apply Herrstedt's combination therapy for treating a highly or moderately emetogenic chemotherapy, such as any of those listed in Table 1. Because the '357 patent does not provide details for implementing its administration for the claimed chemotherapy agents, this further confirms it was within the skills of the POSA to do so. Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy is moderately emetic chemotherapy and where the chemotherapy is any one of carboplatin, cyclophosphamide<1500 mg/m^2, cytarabine>1000 mg/m^2 (which includes cytarabine>1 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, and oxaliplatin, or a combination thereof.

919. Accordingly, it is my opinion that each of claims 9, 12, and 15 as a whole was also obvious over Herrstedt and Bös.

J. Claims 10, 13, 16

> **10.** The method of claim 1, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.
>
> **13.** The method of claim 2, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

> **16.** The method of claim 4, wherein said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, cisplatin, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

920. Each of claims 10, 13, and 16 depends from independent claims 1, 2, and 4, respectively, and additionally recites said chemotherapy is selected from the group consisting of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, carmustine, ***cisplatin***, dacarbazine, dactinomycin, mechlorethamine, streptozotocin, oxaliplatin and combinations thereof.

921. As I previously addressed above, each of claims 1, 2, and 4 was obvious over the combination of Herrstedt and Bös. *See* Sections XXIII.A-XXIII.C, above.

922. Herrstedt discloses treating CINV where the chemotherapy includes cisplatin. Herrstedt discloses its antiemetic drug combination is administered to treat CINV where the chemotherapy is highly or moderately emetic chemotherapy. More specifically, Herrstedt summarizes examples where the chemotherapy is ***cisplatin***. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based***, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as ‘no emesis and no rescue therapy on days 1–5

postcisplatin', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described above in Herrstedt evaluating the antiemetic combination are used to treat CINV induced the chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

923. Herrstedt is not limited to treating CINV where the chemotherapy is cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting from other chemotherapeutic agents. The NK_1 receptor antagonist "increases the effect of a $serotonin_3$-receptor antagonist plus a corticosteroid against acute emesis induced by ***highly or moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such highly or moderately emetogenic chemotherapy includes carboplatin, cyclophosphamide, cytarabine>1 mg/m^2 (e.g., cytarabine>1000 mg/m^2), daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, cisplatin, dacarbazine, mechlorethamine, and streptozotocin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy is any one of carboplatin, cyclophosphamide, cytarabine>1 mg/m^2, daunorubicin, doxorubicin, epirubicin, idarubicin, ifosfamide, irinotecan, cisplatin, dacarbazine, mechlorethamine, and streptozotocin, or a combination thereof.

924. Accordingly, it is my opinion that each of claims 10, 13, and 16 as a whole was also obvious over Herrstedt and Bös.

K. Claims 17, 40, 52

17. The method of claim 1, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

40. The method of claim 2, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

52. The method of claim 4, wherein said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

925. Each of claims 17, 40, and 52 depends from independent claims 1, 2, and 4, respectively, and additionally recites said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy.

926. As I previously addressed above, each of claims 1, 2, and 4 was obvious over the combination of Herrstedt and Bös. *See* Sections XXIII.A-XXIII.C, above.

927. Herrstedt defines treatment of CINV as no emetic episodes and no use of rescue medication following chemotherapy. Herrstedt explains that, following chemotherapy, "[c]omplete response, ***defined as 'no emesis and no rescue therapy*** on days 1-5 postcisplatin', was the ***primary end-point in all studies***." EX1010 (Herrstedt), 146. Herrstedt explains that the "complete response" includes both patients "with ***no emesis***" (i.e., no emetic episodes) and "without the need of ***rescue anti-emetics***" (i.e., no use of rescue medication). *Id.*

928. As I explained above (Sections XXIII.A-XXIII.C, Claims 1, 2, 4) Herrstedt describes studies treating CINV with a therapeutically effective amount of the triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. EX1039 (Poli-Bigelli) expressly confirms that Herrstedt's treatment of CINV is defined as no emetic episodes and no use of rescue medication following chemotherapy. EX1039 (Poli-Bigelli), 3092 (following

chemotherapy, the "proportion of patients who achieved a complete response (defined as ***no emetic episodes and no use of rescue therapy***) in the overall study period (Days 1-5) was ***the primary endpoint of the efficacy analysis***."). Hesketh also confirms that Herrstedt's treatment of CINV is defined as no emetic episodes and no use of rescue medication following chemotherapy. EX1037 (Hesketh), 4113 ("The ***primary end point for the efficacy analysis*** was the proportion of patients with complete response, ***defined as no emetic episodes and no rescue therapy*** (ie ***medication*** taken for established nausea or vomiting) overall (day 1 to 5)" after chemotherapy).

929. Accordingly, it is my opinion that each of claims 17, 40, and 52 as a whole was also obvious over Herrstedt and Bös.

L. Claim 53

53. The method of claim 4, wherein:

a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and

b) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

930. Claim 53 depends from independent claim 4 and additionally recites a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and b) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

931. As I previously addressed above, claim 4 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.C, above.

53(a): a) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and

932. I have reproduced above the intravenous regimen (a) element of claim 53. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the intravenous regimen of claim 53(a).

933. Herrstedt teaches an effective amount of the antiemetic regimen is administered in conjunction with administering the chemotherapy. Herrstedt provides a summary of two studies employing the triple anti-emetic drug regimen described above. *See* Claim 4. As discussed above for claim 4, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) and employing palonosetron as the 5-HT_3 receptor (disclosed in Herrstedt) with dexamethasone was an obvious anti-emetic regimen. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

934. A POSA reviewing Herrstedt would have understood that an effective amount of the antiemetic therapeutics is prophylactically administered prior to the chemotherapy—in other words, said therapeutically effective blood levels of 5-HT_3 and NK_1 receptor antagonists are induced by the anti-emetic regimen administered

prior to said chemotherapy. For example, Poli-Bigelli and Hesketh both expressly confirm that the antiemetic combination (NK_1 and 5-HT_3 receptor antagonists with dexamethasone) is administered prior to the emetogenic chemotherapy (e.g., cisplatin). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes prior to cisplatin***, all patients received ***ondansetron and dexamethasone***.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing the NK_1 receptor antagonist (aprepitant) and the 5-HT_3 receptor antagonist (ondansetron) with dexamethasone prior to the emetogenic chemotherapy (cisplatin) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes before cisplatin***, all patients received ***ondansetron*** (infused over 15 minutes) ***and dexamethasone***.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer the therapeutically effective amount of the antiemetic drug combination prior to the chemotherapy, and would have had a

reasonable expectation of success that such dosing would provide relief from emesis.

935. As I explained above, it was obvious to employ netupitant as the NK_1 receptor antagonist and palonosetron as the 5-HT_3 receptor antagonist. Section XXIII.C, above (claim 4). Furthermore, administering to a patient a therapeutically effective amount of palonosetron and netupitant results in inducing in said subject therapeutically effective blood levels of palonosetron and netupitant. Section XXIII.C, above (claim element 4(a)).

936. Herrstedt suggests its triple therapeutic combination can be administered as an intravenous anti-emetic regimen. With regard to palonosetron, Herrstedt indicates only intravenous administration was available at the time of its publication. EX1010 (Herrstedt), Table 3. Poli-Bigelli and Hesketh confirm the 5-HT_3 receptor antagonist of Herrstedt's anti-emetic regimen is administered intravenously. EX1039 (Poli-Bigelli), 3091 ("intravenous ondansetron 32 mg"); EX1037 (Hesketh), 4113 (same). With regard to aprepitant, Herrstedt suggests its NK_1 receptor antagonist can be administered intravenously. As noted above, Herrstedt summarizes studies including Hesketh. Hesketh provides additional details, including that while aprepitant was administered in its study in oral form, another study observed the same antiemetic effect with "its ***intravenously administered*** prodrug." EX1037 (Hesketh), 4118. Additionally, Bös teaches that,

with regard to its NK_1 receptor antagonists—including netupitant—the compounds can be "in the form of pharmaceutical compositions" and administration includes "***parenterally***, e.g. in the form of ***injection solutions***." EX1014 (Bös), 40:52-62. A skilled practitioner would have known that intravenous administration was a common form of parenterally administered medications. *See, e.g.*, EX1050 (Merriam-Webster) (parenteral is administration "occurring outside the intestine" including "administration by intravenous, intramuscular, or subcutaneous injection."). It is therefore my opinion that Bös suggests intravenous administration of netupitant. Finally, with regard to dexamethasone, Herrstedt explained that corticosteroids (e.g., dexamethasone) were administered either intravenously or orally. EX1010 (Herrstedt), 146-147; *see also* EX1013 (MASCC), Tables 3-4 (confirming oral and intravenous dexamethasone).

937. A skilled practitioner would have had good reason to administer each of the therapeutic drugs intravenously. For example, administration intravenously avoids first pass metabolism, resulting in more consistently administered therapeutic and avoiding metabolic degradation. *See, e.g.*, EX1046 (Thummel), 3173 ("When a drug is dosed intravenously, it avoids first-pass metabolism and is generally completely bioavailable to the different tissues of the body."). It was known that "[f]irst-pass metabolism is a common cause of incomplete and variable absolute bioavailability for an orally dosed drug" and "[t]he drug-metabolizing

enzyme CYP3A4 is often implicated in this process." *Id.*, Abstract. As I described above, the skilled practitioner would have reasonably expected each of netupitant and dexamethasone to be substrates of CYP3A4. *See* Section XIX.C, above. Additionally, Herrstedt explains palonosetron is also a substrate of CYP3A4. EX1010 (Herrstedt), 147. Therefore there was good reason to administer each of the therapeutic agents intravenously.

938. The POSA would have understood it was routine to administer the therapeutic agents intravenously. The skilled artisan would have understood that it was routine practice to formulate therapeutic agents in various ways, including intravenously, and that formulating the therapeutic agents for intravenous administration required nothing more than routine experimentation. EX1059 (Li), Abstract, 12-13. Indeed, intravenous formulations are typically one of the first forms of therapeutic delivery developed. *Id.*, 3 & Table 1 ("oral and intravenous administration" recommendations for animal models). The '357 patent admits it was within the skilled practitioner's ability to develop such intravenous administrations. The '357 patent specification never discloses intravenously administered netupitant, palonosetron, or dexamethasone. Instead, insofar as the '357 specification describes intravenous administration, it is solely to state—in full—that:

> Various pharmaceutical compositions can be developed that make use of the combinations described herein. The composition can

> be administered by any appropriate route, for example, orally, parenterally, or intravenously, in liquid or solid form.

EX1002 (’357 patent), 10:31-35. A person of ordinary skill in the art would have understood from the ’357 specification’s threadbare disclosure that it was within the POSA’s own ability to develop and administer such intravenous formulation.

939. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in claim element 53(a).

> **53(b):** b) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

940. I have reproduced above the five day period (b) element of claim 53. It is my opinion that the combination of Herrstedt and Bös teaches or suggests the five day period of claim 53(b).

941. Herrstedt teaches or suggests element 53(a), as I detailed above, with Bös disclosing netupitant. Herrstedt teaches that its NK_1 receptor antagonist regimen is effective to treat CINV over a five day treatment period after chemotherapy:

> Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. ***Complete response, defined as “no emesis and no rescue therapy on days 1-5 postcisplatin,” was the primary end-point in all studies***. Two of the HEC studies used…ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the

> Hesketh study, a complete response of 72.7% in the aprepitant arm versus 53.3% in the control arm was seen[.]

EX1010 (Herrstedt), 146. Herrstedt describes the triple therapy combination is recommended "for ***prevention of acute and delayed nausea and vomiting***." *Id.*, 148 & Table 4 (MASCC guidelines). Poli-Bigelli confirms the Herrstedt regimen is effective to treat CINV for a five day period after chemotherapy. EX1039 (Poli-Bigelli), 3097 ("The addition of aprepitant…improved the control of CINV associated with highly emetogenic cisplatin-based chemotherapy in the overall study period"), *id.*, 3092 ("the overall ***study period (Days 1-5)***"). Similarly, Hesketh confirms this. EX1037 (Hesketh), Abstract ("aprepitant was generally well tolerated and provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy"); *id.* (evaluation was of "***days 1 to 5 postcisplatin***").

942. Accordingly, the combination of Herrstedt and Bös discloses the subject matter recited in claim element 53(b).

943. Thus, it is my opinion that claim 53 as a whole was also obvious over Herrstedt and Bös.

M. Claim 54

54. The method of claim 4, wherein:

> a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy

b) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

944. Claim 54 depends from independent claim 4 and additionally recites a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy; b) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

945. As I previously addressed above, claim 4 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.C, above.

946. Claim limitation 54(a) ("said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy") is identical to the claim limitation of claim 52. I explained above that claim 52 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.K, above. For at least the same reasons, claim limitation 54(a) was obvious over the combination of Herrstedt and Bös.

947. Claim limitation 54(b) ("said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy") and claim limitation 54(c) ("said regimen is effective to treat said CINV for a five day

period after said chemotherapy") are each identical to claim limitations 53(a) and 53(b), respectively. I explained above that claim 53 as a whole, including each of claim limitations 53(a) and 53(b) was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.L, above. For at least the same reasons, claim limitations 54(b) and 54(c) were each obvious over the combination of Herrstedt and Bös.

948. Accordingly, it is my opinion that claim 54 as a whole was also obvious over Herrstedt and Bös.

N. Claim 56

> **56.** The method of claim 54, wherein said chemotherapy is highly emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

949. Claim 56 depends from dependent claim 54 and additionally recites said chemotherapy is highly emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

950. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

951. I explained at length above why administering therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone was obvious in view of the prior art discussed herein. *See* Section XXIII.A, above (claim element 1(a)). I also explained above (and provided a detailed reasoning that) it is my understanding (and the patent applicant agrees) that the claim term "blood levels" of a drug "effective to treat said CINV" is equivalent to a "therapeutically effective amount" of said drug. Section XXIII.C, above (claim 4(a)). For the same reasons, it is my understanding that the claim term "blood levels" that "are effective to treat said CINV during the acute and delayed phases of said CINV" and that "are effective to treat said CINV during the acute phase of said CINV" are equivalent to a "therapeutically effective amount" of the drugs that achieve the corresponding CINV treatment. Accordingly, the prior art teaches, suggest, or renders obvious this element for the same reasons discussed above that it teaches, suggests, or renders obvious oral or intravenous administration of therapeutically effective amounts of palonosetron and netupitant that is effective to treat CINV during the acute and delayed phases of CINV induced by highly emetogenic chemotherapy.

952. Herrstedt expressly discloses multiple studies administering to subjects therapeutically effective amounts of a 5-HT_3 receptor antagonist and an NK_1 receptor antagonist in a combination regimen with dexamethasone. Herrstedt

summarizes multiple studies for antiemetic treatment of patients receiving highly emetogenic chemotherapy, wherein the antiemetic treatment is a triple-drug combination comprising (i) a 5-HT_3 receptor antagonist (e.g., ondansetron), (ii) an NK_1 receptor antagonist (aprepitant), and (iii) dexamethasone. EX1010 (Herrstedt), 146 ("Two of the ***HEC*** studies used an identical design…***ondansetron***, ***dexamethasone*** and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3."). Herrstedt describes benefits to patients receiving the triple-drug antiemetic combination. *Id.* ("a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm" and "complete response rates were 62.7% versus 43.3%" in another study); *id.* ("Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm.").

953. As I describe above, Herrstedt teaches or suggests administering palonosetron as its 5-HT_3 receptor antagonist. Section XXIII.C, above; EX1010 (Herrstedt), 146 & Table 3. I also describe above that though the specific NK_1 receptor antagonist discussed in Herrstedt was aprepitant, not netupitant, Herrstedt teaches that aprepitant was merely "the first drug" in this class of selective NK_1 receptor antagonists and that the POSA would have employed Bös' netupitant into the Herrstedt regimen. Section XXIII.C, above; EX1014 (Bös), 14:31-38, 17:61-18:48 ("a potent and selective antagonist"), 18:60-63 ("a competitive antagonist at

human recombinant NK_1 receptors"), 19:26-30 ("a potent antagonist of NK_1 induced behaviours in gerbil and blocks emesis in ferrets and [S]ancus murinus with similar potency."). I also explain above that a POSA would have had good reason to employ palonosetron and netupitant in the Herrstedt regimen and would have had a reasonable expectation of success. Section XXIII.C, above.

954. Herrstedt describes its method are effective to treat "[c]hemotherapy-induced nausea and vomiting" (CINV) in a subject receiving highly emetogenic cancer chemotherapy. EX1010 (Herrstedt), 143; *id.*, 144 ("Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy."), 146. Herrstedt describes administering its combination therapy to prevent nausea and vomiting "in patients receiving ***cisplatin***-based, ***highly emetogenic chemotherapy***." *Id.*, 146.

955. Herrstedt describes treating CINV during the acute and delayed phases of chemotherapy. Herrstedt explains its triple combination antiemetic improves efficacy "against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours

after chemotherapy. *Id.*, 143. Herrstedt describes studies treating nausea and vomiting with a triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

956. Poli-Bigelli expressly confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of CINV induced by highly emetogenic chemotherapy (cisplatin). EX1039 (Poli-Bigelli), 3096-3097. For example, Poli-Bigelli describes prevention of nausea via improvement of complete response over periods including the acute and delayed phases, and also explains this parameter is a stand-in for the control of nausea:

> In the assessments of complete response over specific periods after cisplatin, the aprepitant regimen provided a ***substantial improvement*** of 14 percentage points over standard therapy in the prevention of ***acute*** symptoms, and a ***highly remarkable improvement*** of about 21 percentage points in the prevention of ***delayed*** CINV.
>
> Because patients were considered treatment failures if they either vomited or took rescue medication to alleviate nausea, ***the complete response endpoint*** not only reflects control of emesis but also indirectly reflects control of nausea.

EX1039 (Poli-Bigelli), 3096. Thus, Poli-Bigelli identified the addition of NK_1 receptor antagonist (aprepitant) as disclosed in Herrstedt's triple therapy

combination was effective to treat CINV during the acute phase of CINV, and especially during the delayed phase of chemotherapy induced nausea and vomiting.

957. Hesketh also confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1037 (Hesketh), 4116-4117. As with Poli-Bigelli, Hesketh explains that Herrstedt's triple therapy combination improved complete response during both acute and delayed phases and that this directly indicated prevention of nausea:

> [T]he addition of a 3-day regimen of aprepitant significantly ***improved complete response*** as compared with standard therapy ***throughout the acute and delayed phases***. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant) was clearly ***both statistically significant and clinically meaningful***, and was particularly marked during the delayed phase.

EX1037 (Hesketh), 4117. Regarding said complete response parameter, "[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (85.4% v 55.8%***; P < .001)." *Id.*, 4115; *see also id.*, Figure 2 (reproduced below).

958. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n

= 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

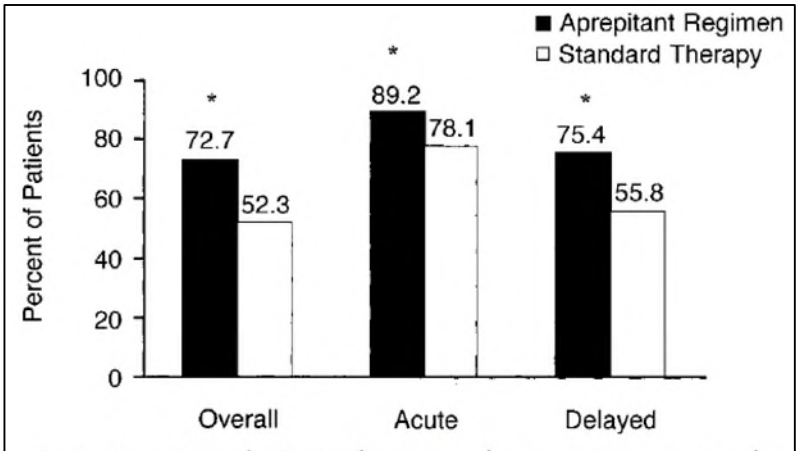


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *P < .001 versus standard therapy.

A POSA would therefore have understood, based on Hesketh's complete response results, that administration of Herrstedt's triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV. Indeed, Hesketh explains that Herrstedt's triple therapy combination ("aprepitant group") was overall superior to the standard therapy (without aprepitant):

> Regardless of the specific end point, ***response rates overall and in the acute and delayed phases were consistently greater*** for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and ***complete protection*** (which ***incorporates both emesis and nausea assessment***), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were ***consistently numerically higher in the aprepitant group***. The higher response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, ***indicate that aprepitant provided some benefit against nausea as well as emesis***.

EX1037 (Hesketh), 4117. Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that administration of the triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV.

959. It was therefore obvious to treat CINV induced by highly emetogenic chemotherapy with a therapeutically effective amount of netupitant and palonosetron, and it was likewise obvious that such therapeutically effective amount would treat CINV during the acute and delayed phases. In other words, it is obvious that such administration would provide netupitant at blood levels effective to treat CINV during the acute and delayed phases, and would also provide palonosetron at blood levels effective to treat CINV during the acute (and delayed) phase of CINV where the CINV is induced by highly emetogenic chemotherapy.

960. Accordingly, it is my opinion that claim 56 as a whole was also obvious over Herrstedt and Bös.

O. Claim 57

> **57.** The method of claim 54, wherein said chemotherapy is moderately emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

961. Claim 57 depends from dependent claim 54 and additionally recites said chemotherapy is moderately emetogenic chemotherapy, said netupitant blood levels are effective to treat said CINV during the acute and delayed phases of said CINV, and said palonosetron blood levels are effective to treat said CINV during the acute phase of said CINV.

962. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

963. I explained at length above why administering therapeutically effective amounts of palonosetron and netupitant in a combination regimen with dexamethasone was obvious in view of the prior art discussed herein. *See* Section XXIII.A, above (claim element 1(a)). I also explained above (and provided a detailed reasoning that) it is my understanding (and the patent applicant agrees) that the claim term "blood levels" of a drug "effective to treat said CINV" is equivalent to a "therapeutically effective amount" of said drug. Section XXIII.C, above (claim 4(a)). For the same reasons, it is my understanding that the claim term "blood levels" that "are effective to treat said CINV during the acute and delayed phases of said CINV" and that "are effective to treat said CINV during the acute phase of said CINV" are equivalent to a "therapeutically effective amount" of the drugs that achieve the corresponding CINV treatment. Accordingly, the prior art teaches, suggest, or renders obvious this element for the same reasons discussed above that it teaches, suggests, or renders obvious oral or intravenous administration of therapeutically effective amounts of palonosetron and netupitant that is effective to treat CINV during the acute and delayed phases of CINV induced by moderately emetogenic chemotherapy.

964. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***"). Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating CINV in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a $serotonin_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to effectively treat CINV where the chemotherapy is moderately emetogenic chemotherapy.

965. Herrstedt discloses its NK_1 antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

966. A POSA reviewing Herrstedt would have understood that the antiemetic regimen is effective to treat CINV during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is

the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to emetogenic chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the

complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to treat CINV during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats CINV during the acute and delayed phases of CINV. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

967. Each of Poli-Bigelli and Hesketh describe triple antiemetic dosing regimen is useful for treating CINV where chemotherapy is cisplatin (highly emetogenic chemotherapy). Nonetheless, a POSA would have reasonably expected similar CINV treatment where the chemotherapy is moderately emetogenic because the mechanism of treatment is the same (e.g., occupancy of NK_1 and 5-

HT_3 receptors). Herrstedt confirms that its regimen is applicable for treating both highly emetogenic and moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract.

968. Therefore, a POSA would have had good reason to prophylactically administer the drug regimen of Herrstedt, employing netupitant from Bös, palonosetron from Herrstedt, and would have had a reasonable expectation of success that such dosing would effectively treat CINV during the acute and delayed phases of CINV induced by moderately emetogenic chemotherapy. In other words, it is obvious that such administration would provide netupitant at blood levels effective to treat CINV during the acute and delayed phases, and would also provide palonosetron at blood levels effective to treat CINV during the acute (and delayed) phase of CINV where the CINV is induced by moderately emetogenic chemotherapy.

969. Accordingly, it is my opinion that claim 57 as a whole was also obvious over Herrstedt and Bös.

P. Claim 58

> **58.** The method of claim 54, wherein said chemotherapy is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

970. Claim 58 depends from dependent claim 54 and additionally recites said chemotherapy is highly emetogenic chemotherapy, and said regimen is

effective to prevent or reduce the severity of nausea during the acute and delayed phases.

971. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

972. Herrstedt discloses a regimen for treating chemotherapy-induced nausea and vomiting (CINV) wherein the chemotherapy is highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"). Herrstedt discloses its NK_1 antiemetic combination provides therapeutic effect for "emesis induced by highly or moderately emetogenic chemotherapy" noting in particular that the NK_1 receptor antagonist is "also active in the protection against delayed emesis." *Id.*, Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

973. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was used to treat nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy, and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy.

EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
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Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly***

reflects control of nausea" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (i.e., cisplatin) and is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

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Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

974. Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös and palonosetron from Herrstedt, and would have had a reasonable expectation of

success that such dosing would treat CINV wherein the chemotherapy is highly emetogenic chemotherapy (e.g., cisplatin) and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases of CINV.

975. Accordingly, it is my opinion that claim 58 as a whole was also obvious over Herrstedt and Bös.

Q. Claim 59

> **59.** The method of claim 54, wherein said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

976. Claim 59 depends from dependent claim 54 and additionally recites said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

977. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

978. Herrstedt suggests the chemotherapy is moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

979. Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
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Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy is moderately emetogenic chemotherapy.

980. Herrstedt discloses its triple antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

981. A POSA reviewing Herrstedt would have understood that the antiemetic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and

vomiting in response to emetogenic chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

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No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
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[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt

treats nausea and vomiting where the emesis inducing event is chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

982. Each of Poli-Bigelli and Hesketh describe the NK_1 receptor antagonist dosing regimen is useful for preventing or reducing the severity of nausea where chemotherapy is cisplatin (highly emetogenic chemotherapy). Nonetheless, a POSA would have reasonably expected similar anti-nausea effect for treatment of nausea where the chemotherapy is moderately emetogenic because the mechanism of treatment is the same (e.g., occupancy of NK_1 and 5-HT_3 receptors). Herrstedt confirms that its regimen is applicable for treating both highly emetogenic and moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract.

983. Therefore, a POSA would have had good reason to prophylactically administer the drug regimen of Herrstedt, employing netupitant from Bös, the palonosetron from Herrstedt, and would have had a reasonable expectation of success that such dosing would treat nausea and vomiting wherein chemotherapy is moderately emetogenic chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

984. Accordingly, it is my opinion that claim 59 as a whole was also obvious over Herrstedt and Bös.

R. Claims 60-61

> **60.** The method of claim 54, wherein said chemotherapy comprises cisplatin.
>
> **61.** The method of claim 54, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

985. Each of claims 60 and 61 depends from dependent claim 54 and additionally recites that said chemotherapy comprises cisplatin (claim 60) or comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 61).

986. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

987. Herrstedt discloses the chemotherapy comprises cisplatin. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a

combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

988. Additionally, as I explained above, Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. EX1010 (Herrstedt), Abstract. Herrstedt suggests treating CINV wherein the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy comprises

cisplatin (as in claim 60) and where the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (as in claim 61).

989. Accordingly, it is my opinion that each of claims 60-61 as a whole were also obvious over Herrstedt and Bös.

S. Claim 62

62. The method of claim 54, wherein said chemotherapy comprises cyclophosphamide.

990. Claim 62 depends from dependent claim 54 and additionally recites that said chemotherapy comprises cyclophosphamide.

991. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIII.M, above.

992. Herrstedt discloses treating CINV where the chemotherapy comprises highly or moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***"). Herrstedt identifies that the NK_1 receptor antagonist is broadly applicable to treating chemotherapy-induced nausea and vomiting.

993. Herrstedt describes cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

994. Thus, a POSA would have understood Herrstedt to suggest that its antiemetic drug combination is administered to treat CINV induced by highly or moderately emetogenic chemotherapy, where the chemotherapy is cyclophosphamide.

995. Accordingly, it is my opinion that claim 62 as a whole was also obvious over Herrstedt and Bös.

T. Motivation to Combine

996. As I describe above, by November 18, 2009, a person having ordinary skill in the art would have had good reason to treat chemotherapy induced nausea and vomiting in a subject receiving emetogenic chemotherapy. The POSA would have achieved such effects by inducing in said subject therapeutically effective blood levels of palonosetron and netupitant (e.g., by administering to the subject receiving chemotherapy a regimen of therapeutically effective amounts of

palonosetron, netupitant, and dexamethasone) in a combination regimen with dexamethasone (e.g., administered in a sub-therapeutic dose). *See* Sections XXIII.A-XXIII.C, above. I described that persons having ordinary skill in the art would have had good reason to treat patients receiving emetogenic chemotherapy with therapeutically effective amounts of the Herrstedt triple therapy to provide antiemetic effect. *Id.*; *see also* EX1016 (Herrington), Abstract, 2084 (5-HT_3 and NK_1 receptor antagonists administered with dexamethasone provided antiemetic effect). Additionally, I explained that a person having ordinary skill in the art would have modified the Herrstedt triple therapy to include the new 5-HT_3 receptor antagonist, palonosetron.

997. The person having ordinary skill in the art also would have modified the Herrstedt triple therapy to include the second generation NK_1 receptor antagonist, netupitant. The POSA would have expected continued efficacy of the therapeutic combination of Herrstedt with new drugs targeting the same mechanistic pathway—e.g., antagonism of the NK_1 receptor. The POSA thus would have had good reason to modify the Herrstedt antiemetic drug combination to replace NK_1 receptor antagonist aprepitant with Bös' NK_1 receptor antagonist netupitant ("formula Ib") because, as Bös explains, netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK_1 receptor-induced foot tapping after oral administration, which was indicative of

successful NK_1 receptor antagonism. EX1014 (Bös), 14:32-19:37, Sections XXIII.A-XXIII.C, above. Bös provided in vivo studies including evaluation of blocking emesis (*id.*, 19:10-30) and identified netupitant had a long half-life and high bioavailability (*id.*, 19:31-37). Additionally, Bös provided a dosing range of about 10 to about 1,000 mg (*id.*, 42:5-11). Thus, netupitant was known to be a second generation NK_1 receptor antagonist, and the POSA would have sought to modify Herrstedt by replacing aprepitant with a therapeutically effective amount of netupitant, and would have had a reasonable expectation of success in doing so.

998. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new 5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving emetogenic chemotherapy. For the same reasons, the POSA would have had good reason to induce in patients receiving chemotherapy blood levels of palonosetron and netupitant effective to treat CINV—which the POSA would have reasonably expected was the natural result of administering the therapeutically effective amount. *See* Section XXIII.C. Finally, as I explained above, the POSA would have had good reason to administer a sub-therapeutic dose of dexamethasone (i.e., in a dose amount lower than would be used if dexamethasone were administered as a monotherapy). *See* Section XXIII.B.

U. Reasonable Expectation of Success

999. As I explained above, a person having ordinary skill in the art before November 18, 2009, would have had a reasonable expectation of success in modifying the Herrstedt triple active combination therapy with the claimed netupitant and palonosetron therapeutics. *See* Sections XXIII.A-XXIII.C, above. I explained, for example, that the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a new, preferred 5-HT_3 receptor antagonist (palonosetron) for an older 5-HT_3 receptor antagonist (ondansetron) would work in the same manner to achieve a similar (or improved) outcome.

1000. Similarly, the person having ordinary skill in the art would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome. Herrstedt recognized that aprepitant was "the first drug" belonging to a "new group of anti-emetics, the neurokinin1-receptor antagonists" being developed. EX1010 (Herrstedt), Abstract. Both netupitant and aprepitant were known to be therapeutically effective via the same mechanism—by antagonizing the NK_1 receptor. EX1014 (Bös), 14:31-38 ("a highly selective antagonist"), 18:42-48 ("a potent and selective antagonist"). Thus, a POSA would have expected

therapeutically effective amounts of aprepitant and netupitant to achieve at least comparable effect of anti-emesis. That netupitant was known to have favorable qualities as compared to aprepitant (as I describe above) means the POSA would have reasonably expected that netupitant would be clinically comparable to or better to the Herrstedt antiemetic drug combination using aprepitant. Additionally, because each of the drugs in Herrstedt's triple combination targets a different mechanism providing relief for a patient suffering from nausea and vomiting, a POSA would have had a reasonable expectation of success in further improving both nausea and vomiting following CINV during both the acute and delayed period when the triple therapy was administered.

1001. The POSA would have had a reasonable expectation that administration of the therapeutically effective dose would result in inducing in the patient therapeutically effective blood levels of palonosetron and netupitant effective to treat CINV. As I explain above, the claim term "blood levels" of a drug "effective to treat said CINV" is equivalent to a "therapeutically effective amount" of said drug. Section XXIII.C, above. Additionally, "inducing" the effective blood levels is equivalent to administering the therapeutically effective amount in any manner that operates via the blood, which includes oral and intravenous administration (both methods known in the prior art). *Id.*

1002. Accordingly, the POSA had good reason to combine Herrstedt and Bös to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXIV. ['357 PATENT GROUND 2] '357 PATENT CLAIMS 18-19, 25-27, 30-32, AND 41-42 WERE OBVIOUS OVER HERRSTEDT, BÖS, AND OPTIONALLY HERRINGTON

1003. For the reasons discussed in detail below, it is my opinion that each of claims 18-19, 25-27, 30-32, and 41-42 of the '357 patent was obvious as a whole. The obviousness of claims 18-19, 25-27, 30-32, and 41-42 is exemplified by disclosures in the Herrstedt, Bös, and optionally Herrington references.

1004. I have evaluated below whether the combination of Herrstedt, Bös, and optionally Herrington discloses each and every element of each of claims 18-19, 25-27, 30-32, and 41-42 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 18

18. The method of claim 1, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1005. Claim 18 depends from independent claim 1 and additionally recites a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof; b) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1006. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.A, above.

1007. Herrstedt discloses its triple therapeutic regimen includes a single administration of NK_1 receptor antagonist prophylactically administered on day one of the five day treatment period. Herrstedt explains its aprepitant NK_1 receptor antagonist is administered on days one, two, and three:

Two of the HEC studies used an identical design comparing

> ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3….

EX1010 (Herrstedt), 146. A POSA reviewing Herrstedt would have understood that the regimen it discusses includes a single administration of its NK_1 receptor antagonist prophylactically administered on day one.

1008. The combination of Herrstedt and Bös suggests a single administration of netupitant is administered without administering a second dose of netupitant for at least five consecutive days, and that the treatment regimen is effective to treat CINV during the five day period after chemotherapy. Herrstedt describes administering aprepitant on days one, two, and three of the five consecutive days. EX1010 (Herrstedt), 146. But as I explained above (Claim 1), the POSA had good reason to substitute Bös' netupitant for Herrstedt's aprepitant. Netupitant was known to have a large half-life value, thus reducing any need for subsequent administrations of NK_1 receptor antagonist. EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). The POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination provided further reason to omit subsequent doses of NK_1 receptor antagonist because a single dose would sustain therapeutic efficacy. In other words, the POSA would have understood a single day one dose of netupitant to be effective to treat CINV

for the five consecutive days—the therapeutic period evaluated by the studies summarized in Herrstedt. Thus, the combination of Herrstedt and Bös suggests a single administration of netupitant is administered on day one of a five day treatment period, where no further netupitant is administered during said five days (i.e., without administering a second dose of netupitant for at least five days).

1009. Herrington confirms a single dose of NK_1 receptor antagonist administered prophylactically on day one of said five consecutive days, where no further NK_1 receptor antagonist is administered during a five day treatment period (i.e., without administering a second dose), is effective to treat CINV for the five day period after chemotherapy. Herrington teaches a single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. Herrington describes that:

> The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy….
>
> From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

EX1016 (Herrington), Background. A POSA thus would have understood that the single administration of an NK_1 receptor antagonist on day one was similarly

effective to the dosing protocol of Herrstedt dosing the NK_1 receptor antagonist on multiple days. Herrington reports this efficacy (to treat said nausea and vomiting) was evaluated across the entire five day period. EX1016 (Herrington), 2081 ("The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy."). Herrington reports the single day one dose of NK_1 receptor antagonist is effective to treat CINV for five consecutive days:

> There were no significant differences between Arms A [3-day aprepitant] and B [single day one dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In ***Arms*** A and ***B, 93% of patients were emesis-free from Days 1-5*** compared with only 50% in Arm C [control group].

EX1016 (Herrington), Abstract. Herrington describes that the single administration of NK_1 receptor antagonist also provided control against nausea across the five day period. *Id.*, 2086 ("The control of nausea was achieved in similar fashion between the 2 aprepitant arms."). Although Herrington identified "a trend toward better significant nausea on Days 4-5 with the 3-day Arm A versus the single dose" the mean severity of nausea for the single dose of aprepitant was lower than the control test group across all five days. *Id.*, 2086, 2084 & Table 4 (reproduced below).

TABLE 4
Severity of Nausea Using VAS

	Severity of nausea using VAS (mean±SD; median, range)			
	Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	*P*[*]	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0–95)	8.7 ± 15.7 0(0–60)	.82	15.6 ± 32.1 0(0–95)
Day 2	15.2 ± 24.6 4(0–95)	11.0 ± 16.1 1(0–50)	.80	28.4 ± 39.2 2.5(0–100)
Day 3	15.0 ± 26.1 1.5(0–95)	12.3 ± 16.5 2.5(0–50)	.95	30.3 ± 40.4 2.5(0–100)
Day 4	10.5 ± 21.8 3.5(0–95)	16.6 ± 23.6 2.5(0–75)	.62	19.6 ± 31.5 2.5(0–95)
Day 5	12.0 ± 25.2 0(0–95)	18.3 ± 27.2 0(0–80)	.52	20.6 ± 34.0 0(0–95)

VAS indicates visual analog scale; SD, standard deviation.
* Wilcoxon 2-sample test, (3-Day vs 1-Day).

Thus, Herrington confirms its single administration of aprepitant, where no further NK_1 receptor antagonist is administered during the five day period, is effective to treat nausea and vomiting for the five consecutive days.

1010. A POSA would have been motivated to use a single dose of aprepitant as disclosed by Herrington in Herrstedt's triple therapeutic combination for decreased costs, increased convenience, and patient preference for single administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would have had good reason to employ the single prophylactic dose of NK_1 receptor antagonist in the dosing protocol of Herrstedt without dosing on subsequent days.

As discussed above, the POSA would have employed Bös' second generation NK_1 receptor antagonist—netupitant—in Herrstedt's protocol.

1011. Herrstedt also discloses its regimen comprises a single prophylactic administration of the 5-HT_3 receptor antagonist (e.g., palonosetron, ondansetron) without administering a second dose of palonosetron, where the regimen is effective to treat CINV for a five day period after chemotherapy. Herrstedt explains:

> Complete response, defined as 'no emesis and no rescue therapy on ***days 1–5 postcisplatin***', was the primary end-point in all studies. Two of the HEC studies used an identical design comparing ***ondansetron***, dexamethasone and placebo ***day 1*** followed by dexamethasone plus placebo days 2–4 with ***ondansetron***, dexamethasone and aprepitant ***day 1*** followed by dexamethasone days 2–4 plus aprepitant days 2–3.

EX1010 (Herrstedt), 146. In other words, the 5-HT_3 receptor antagonist ondansetron was prophylactically administered only on day one (i.e., there was only one administration of the 5-HT_3 receptor antagonist during the five days). Herrstedt summarizes that the field had embraced administering the 5-HT_3 receptor antagonist in a single dose across the five day period, and suggests that palonosetron should be used as the 5-HT_3 receptor antagonist:

> Ondansetron and granisetron were initially developed as 8 mg t.i.d. and 3 mg plus up to two additional doses within the first 24 hr after chemotherapy, respectively. ***Today, all these agents are primarily***

used as a single oral or intravenous dose (ondansetron can be given twice daily in patients receiving MEC). Originally ondansetron and granisetron were prescribed for up to 5 days after chemotherapy, but it is now recognized that the 5-HT3-receptor antagonists are primarily effective in the prophylaxis of acute emesis with limited or no efficacy in delayed emesis. ***Palonosetron might be an exception and it has been approved by the Food and Drug Administration*** (but not by the European Medicines Agency) ***in the treatment of delayed emesis*** from MEC.

Id., 145-146.

1012. Furthermore, the POSA would have understood that the increased half-life of palonosetron indicated that the single dose of palonosetron on day 1 of therapy (prior to chemotherapy) would be sufficient to confer the delayed emesis benefit provided by palonosetron. Herrstedt describes that palonosetron has an ***order of magnitude*** greater half-life as compared to ondansetron. *Id.*, Table 3 (below).

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

Therefore, the POSA would have had good reason to prophylactically administer a

single administration of palonosetron or a pharmaceutically acceptable salt thereof during the five day treatment period.

1013. Herrstedt discloses the NK_1 receptor antagonist and 5-HT_3 receptor antagonist are administered in concomitantly with the chemotherapy. Herrstedt summarizes two studies administering the triple antiemetic drug combination described above. EX1010 (Herrstedt), 146. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." *Id.* (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)). A POSA reviewing Herrstedt would have understood that the NK_1 and 5-HT_3 receptor antagonists are administered no more than one hour prior to administration of the chemotherapy, which the POSA would have understood to be concomitant administration prior to chemotherapy. *See, e.g.*, EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist administered one hour prior to cisplatin; 5-HT_3 receptor antagonist administered thirty minutes prior to cisplatin); EX1037 (Hesketh), 4113 (same). Poli-Bigelli and Hesketh both expressly confirm that the NK_1 receptor antagonist and 5-HT_3 receptor antagonist are administered no more than one hour prior to administration of the chemotherapy. Poli-Bigelli describes, with regard to its timing:

> One hour prior to cisplatin, patients received either aprepitant or placebo. Thirty minutes prior to cisplatin, all patients received ondansetron and dexamethasone.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing aprepitant one hour prior to administration of cisplatin (and in combination with the other drugs disclosed in the regimen) "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> One hour before cisplatin, patients received either aprepitant or placebo. Thirty minutes before cisplatin, all patients received ondansetron (infused over 15 minutes) and dexamethasone.

EX1037 (Hesketh), 4113. Thus, a POSA would have had good reason to administer the NK_1 receptor antagonist and 5-HT_3 receptor antagonist concomitantly and prior to chemotherapy, and would have had a reasonable expectation of success that such dosing would be effective to treat CINV. As I explained above, the POSA also would have had good reason to employ netupitant as the NK_1 receptor antagonist and palonosetron as the 5-HT_3 receptor antagonist, and would have had a reasonable expectation that employing them concomitantly and prior to chemotherapy would also provide the treatment of CINV throughout the treatment period of five days (e.g., due to similar treatment profiles and mechanisms of action).

1014. Accordingly, it is my opinion that claim 18 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

B. Claim 19

19. The method of claim 1, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;

c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and

d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1015. Claim 19 depends from independent claim 1 and additionally recites a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy; b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof; c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1016. As I previously addressed above, claim 1 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.A, above.

1017. Claim limitation 19(a) ("said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy") is identical to the claim limitation of claim 17. I explained above that claim 17 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.K, above. For at least the same reasons, claim limitation 19(a) was obvious over the combination of Herrstedt, Bös, and optionally Herrington.

1018. Claim limitation 19(b) ("said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof"), claim limitation 19(c) ("said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy"), and claim limitation 19(d) ("said regimen is effective to treat said CINV for a five day period after said chemotherapy") are each identical to claim limitations 18(a), 18(b), and 18(c), respectively. I explained above that claim 18 as a whole, including each of claim limitations 18(a), 18(b), and 18(c), was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.A, above. For at least the same

reasons, claim limitations 19(b), 19(c), and 19(d) were each obvious over the combination of Herrstedt, Bös, and optionally Herrington.

1019. Accordingly, it is my opinion that claim 19 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

C. Claim 25

25. The method of claim 19, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1020. Claim 25 depends from dependent claim 19 and additionally recites a) said chemotherapy is highly emetogenic chemotherapy; and b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1021. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1022. Herrstedt discloses a method for preventing "[c]hemotherapy-induced nausea and vomiting" (CINV) in a subject receiving highly emetogenic cancer chemotherapy by administering an antiemetic drug combination. EX1010 (Herrstedt), 143; *id.*, 144 ("Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy."), 146. Herrstedt

describes administering its combination therapy to prevent nausea and vomiting "in patients receiving ***cisplatin***-based, ***highly emetogenic chemotherapy***." *Id.*, 146.

1023. Herrstedt describes treating CINV during the acute and delayed phases of chemotherapy. Herrstedt explains its triple combination antiemetic improves efficacy "against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Herrstedt describes studies treating nausea and vomiting with a triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1024. Poli-Bigelli expressly confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of CINV induced by highly emetogenic chemotherapy (cisplatin). EX1039 (Poli-Bigelli), 3096-3097. For example, Poli-Bigelli describes prevention of nausea via improvement of complete response over periods including the acute and delayed phases, and also explains this parameter is a stand-in for the control of nausea:

In the assessments of complete response over specific periods after

> cisplatin, the aprepitant regimen provided a ***substantial improvement*** of 14 percentage points over standard therapy in the prevention of ***acute*** symptoms, and a ***highly remarkable improvement*** of about 21 percentage points in the prevention of ***delayed*** CINV.
>
> Because patients were considered treatment failures if they either vomited or took rescue medication to alleviate nausea, ***the complete response endpoint*** not only reflects control of emesis but also indirectly reflects control of nausea.

EX1039 (Poli-Bigelli), 3096. Thus, Poli-Bigelli identified the addition of NK_1 receptor antagonist (aprepitant) as disclosed in Herrstedt's triple therapy combination was effective to treat CINV during the acute phase of CINV, and especially during the delayed phase of chemotherapy induced nausea and vomiting.

1025. Hesketh also confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1037 (Hesketh), 4116-4117. As with Poli-Bigelli, Hesketh explains that Herrstedt's triple therapy combination improved complete response during both acute and delayed phases and that this directly indicated prevention of nausea:

> [T]he addition of a 3-day regimen of aprepitant significantly ***improved complete response*** as compared with standard therapy ***throughout the acute and delayed phases***. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant)

> was clearly ***both statistically significant and clinically meaningful***, and was particularly marked during the delayed phase.

EX1037 (Hesketh), 4117. Regarding said complete response parameter, "[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (85.4% v 55.8%***; P < .001)." *Id.*, 4115; *see also id.*, Figure 2 (reproduced below).

1026. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

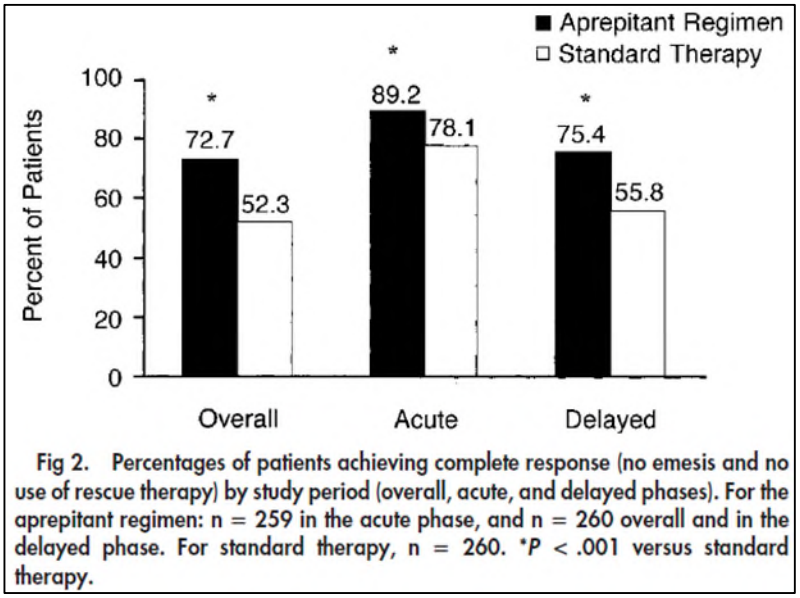


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *$P < .001$ versus standard therapy.

A POSA would therefore have understood, based on Hesketh's complete response results, that administration of Herrstedt's triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV. Indeed, Hesketh explains that Herrstedt's triple therapy combination ("aprepitant group") was overall superior to the standard therapy (without aprepitant):

> Regardless of the specific end point, ***response rates overall and in the acute and delayed phases were consistently greater*** for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and ***complete protection*** (which ***incorporates both emesis and nausea assessment***), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were ***consistently numerically higher in the aprepitant group***. The higher

> response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, ***indicate that aprepitant provided some benefit against nausea as well as emesis***.

EX1037 (Hesketh), 4117. Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that administration of the triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV.

1027. Accordingly, it is my opinion that claim 25 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

D. Claim 26

26. The method of claim 19, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1028. Claim 26 depends from dependent claim 19 and additionally recites a) said chemotherapy is highly emetogenic chemotherapy; and b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1029. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1030. Herrstedt discloses a regimen for treating chemotherapy-induced nausea and vomiting (CINV) wherein the chemotherapy is highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"). Herrstedt discloses its NK_1 antiemetic combination provides therapeutic effect for "emesis induced by highly or moderately emetogenic chemotherapy" noting in particular that the NK_1 receptor antagonist is "also active in the protection against delayed emesis." *Id.*, Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1031. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was used to treat nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy, and the regimen is effective to prevent nausea or reduce the severity of nausea in patients during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy,

while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is

effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (i.e., cisplatin) and is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

1032. Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, the palonosetron of Herrstedt, and would have had a reasonable expectation of success that such dosing would treat CINV wherein the chemotherapy is highly emetogenic chemotherapy (e.g., cisplatin) and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases of CINV.

1033. Accordingly, it is my opinion that claim 26 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

E. Claim 27

27. The method of claim 19, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1034. Claim 27 depends from dependent claim 19 and additionally recites a) said chemotherapy is moderately emetogenic chemotherapy; and b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1035. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1036. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. Herrstedt, Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***"). Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to

treating CINV in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

It would have been within a POSA's skill and abilities to apply Herrstedt's combination therapy for treating a highly or moderately emetogenic chemotherapy, such as any of those listed in Table 1. Because the '357 patent does not provide an example for implementing its administration for MEC, this further confirms it was within the skills of the POSA to do so. Thus, a POSA would have understood

Herrstedt to disclose its antiemetic drug combination is administered to effectively treat CINV where the chemotherapy is moderately emetogenic chemotherapy.

1037. Herrstedt discloses its NK_1 antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1038. A POSA reviewing Herrstedt would have understood that the antiemetic regimen is effective to prevent nausea or reduce the severity of nausea during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to emetogenic chemotherapy

during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent nausea or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is

chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

1039. Each of Poli-Bigelli and Hesketh describe the NK_1 receptor antagonist dosing regimen is useful for preventing or reducing the severity of nausea where chemotherapy is cisplatin (highly emetogenic chemotherapy). Nonetheless, a POSA would have reasonably expected similar anti-nausea effect for treatment of nausea where the chemotherapy is moderately emetogenic because the mechanism of treatment is the same (e.g., occupancy of NK_1 and 5-HT_3 receptors). Herrstedt confirms that its regimen is applicable for treating both highly emetogenic and moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract.

1040. Therefore, a POSA would have had good reason to prophylactically administer the drug regimen of Herrstedt, employing netupitant from Bös,

palonosetron from Herrstedt, and would have had a reasonable expectation of success that such dosing would effectively treat CINV during the acute and delayed phases of CINV induced by moderately emetogenic chemotherapy.

1041. Accordingly, it is my opinion that claim 27 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

F. Claims 30-31

> **30.** The method of claim 19, wherein said chemotherapy comprises cisplatin.
>
> **31.** The method of claim 19, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

1042. Each of claims 30 and 31 depends from dependent claim 19 and additionally recites that said chemotherapy comprises cisplatin (claim 30) or comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 31).

1043. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1044. Herrstedt discloses the chemotherapy comprises cisplatin. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

1045. Additionally, as I explained above, Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. EX1010 (Herrstedt), Abstract. Herrstedt suggests treating CINV wherein the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy comprises cisplatin (as in claim 30) and where the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (as in claim 31).

1046. Accordingly, it is my opinion that each of claims 30-31 as a whole were also obvious over Herrstedt, Bös, and optionally Herrington.

G. Claim 32

32. The method of claim 19, wherein said chemotherapy comprises cyclophosphamide.

1047. Claim 32 depends from dependent claim 19 and additionally recites that said chemotherapy comprises cyclophosphamide.

1048. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1049. Herrstedt discloses treating CINV where the chemotherapy comprises highly or moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***"). Herrstedt identifies that the NK_1 receptor antagonist is broadly applicable to treating chemotherapy-induced nausea and vomiting.

1050. Herrstedt describes cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

1051. Thus, a POSA would have understood Herrstedt to suggest that its antiemetic drug combination is administered to treat CINV induced by highly or moderately emetogenic chemotherapy, where the chemotherapy is cyclophosphamide.

1052. Accordingly, it is my opinion that claim 32 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

1053.

H. Claim 41

41. The method of claim 2, wherein:

a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of

dexamethasone without administering a second dose for at least five days after said chemotherapy;

d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1054. Claim 41 depends from independent claim 2 and additionally recites that a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy; b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy; c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy; d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy; e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior

to said chemotherapy; f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1055. As I previously addressed above, claim 2 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.B, above.

> **41(a):** a) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

1056. I have reproduced above the single administration (a) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the single administration of claim 41(a).

1057. Herrstedt discloses a single dose of NK_1 receptor antagonist is administered on day one of said five consecutive days. Herrstedt explains its aprepitant NK_1 receptor antagonist is administered on days one, two, and three:

> Two of the HEC studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2-4 with ondansetron, dexamethasone and ***aprepitant day 1*** followed by dexamethasone days 2-4 plus aprepitant days 2-3….

EX1010 (Herrstedt), 146. As I explained above, a POSA would have had good reason to employ Bös' netupitant as the NK_1 receptor antagonist in Herrstedt's dosing regimen.

1058. The combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of a five-day treatment period, without administering a second dose for at least the five days after chemotherapy. Netupitant was known to have a large half-life value, thus reducing any need for subsequent administrations of NK_1 receptor antagonist. EX1014 (Bös), 19:3-10 (functional half-life of 30 hours). The POSA would have understood that substitution of netupitant into Herrstedt's antiemetic drug combination provided further reason to omit subsequent doses of NK_1 receptor antagonist because a single dose would sustain therapeutic efficacy. In other words, the POSA would have understood a single day one dose of netupitant to be effective to treat nausea and vomiting for five consecutive days following chemotherapy. Thus, the combination of Herrstedt and Bös suggests a single dose of netupitant is administered on day one of a five day treatment period, no further netupitant is administered during said five days, and said single dose of netupitant is effective to treat said nausea and vomiting for said five days.

1059. Herrington confirms a single dose of NK_1 receptor antagonist administered on day one of said treatment period of five days, where no further NK_1 receptor antagonist is administered during said five days, is effective to treat nausea and vomiting for the five days after chemotherapy. Herrington teaches a

single dose of aprepitant provided similar effectiveness as compared to Herrstedt's protocol of dosing aprepitant three times. Herrington describes that:

> The purpose of this pilot study was to ***ascertain the effectiveness of 1-day versus 3-day aprepitant*** in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy….
>
> From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a ***single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant***.

EX1016 (Herrington), Background. A POSA thus would have understood that the single administration of an NK_1 receptor antagonist on day one was similarly effective to the dosing protocol of Herrstedt dosing the NK_1 receptor antagonist on multiple days. Herrington reports efficacy (to treat said nausea and vomiting) was evaluated across the entire five day period. EX1016 (Herrington), 2081 ("The primary efficacy endpoint was the proportion of patients with emesis in the acute (Day 1) and delayed (Days 2-5) phases after chemotherapy."). Herrington reports the single day one dose of NK_1 receptor antagonist is effective to treat said nausea and vomiting for said five consecutive days:

> There were no significant differences between Arms A [3-day aprepitant] and B [single day one dose aprepitant] for emesis, nausea, or the use of break-through antiemetics. In ***Arms*** A and ***B, 93% of patients were emesis-free from Days 1-5*** compared with only 50% in

Arm C [control group].

EX1016 (Herrington), Abstract. Herrington describes that the single prophylactic day one dose of NK_1 receptor antagonist provided control against nausea across the five day period. *Id.*, 2086 ("The control of nausea was achieved in similar fashion between the 2 aprepitant arms."). Although Herrington identified "a trend toward better significant nausea on Days 4-5 with the 3-day Arm A versus the single dose" the mean severity of nausea for the single dose of aprepitant was lower than the control test group across all five days. *Id.*, 2086, 2084 & Table 4 (reproduced below).

TABLE 4
Severity of Nausea Using VAS

Severity of nausea using VAS (mean±SD; median, range)				
	Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	*P**	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0–95)	8.7 ± 15.7 0(0–60)	.82	15.6 ± 32.1 0(0–95)
Day 2	15.2 ± 24.6 4(0–95)	11.0 ± 16.1 1(0–50)	.80	28.4 ± 39.2 2.5(0–100)
Day 3	15.0 ± 26.1 1.5(0–95)	12.3 ± 16.5 2.5(0–50)	.95	30.3 ± 40.4 2.5(0–100)
Day 4	10.5 ± 21.8 3.5(0–95)	16.6 ± 23.6 2.5(0–75)	.62	19.6 ± 31.5 2.5(0–95)
Day 5	12.0 ± 25.2 0(0–95)	18.3 ± 27.2 0(0–80)	.52	20.6 ± 34.0 0(0–95)

VAS indicates visual analog scale; SD, standard deviation.
* Wilcoxon 2-sample test, (3-Day vs 1-Day).

Thus, Herrington confirms its single dose of aprepitant administered on day one, where no further NK_1 receptor antagonist is administered during the five day period, is effective to treat nausea and vomiting for the five consecutive days.

1060. A POSA would have been motivated to use a single dose of NK_1 receptor antagonist as disclosed by Herrington in Herrstedt's therapeutic combination for decreased costs, increased convenience, and patient preference for single administration. *See* Section IX.G, above. Thus, it is my opinion that a POSA would have had good reason to employ the single dose of NK_1 receptor antagonist in the dosing protocol of Herrstedt without dosing on subsequent days. As discussed above, the POSA would have employed Bös' second generation NK_1 receptor antagonist—netupitant—in Herrstedt's protocol.

1061. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(a).

> **41(b):** b) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

1062. I have reproduced above the moderately or highly emetogenic (b) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the moderately or highly emetogenic element of claim 41(b).

1063. Herrstedt discloses the chemotherapy comprises moderately or highly emetogenic chemotherapy. As detailed above, Herrstedt discloses its antiemetic

drug combination is administered for treatment of chemotherapy induced nausea and vomiting (CINV). *See* Claim 1, above. Herrstedt also describes efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***." EX1010 (Herrstedt), Abstract. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of ***cyclophosphamide plus an anthracycline***. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Herrstedt also includes a table of chemotherapies and classifies cisplatin as highly emetogenic. *Id.*, Table 1. Another of Herrstedt's tables categorizes the cyclophosphamide and anthracycline combination chemotherapy as between highly emetogenic and moderately emetogenic. *Id.*, Table 4. Thus, the studies described above in Herrstedt evaluating the antiemetic combination to treat CINV are used to treat nausea and vomiting induced by moderately or highly emetogenic chemotherapy. EX1010 (Herrstedt), 146, Abstract.

1064. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(b).

> **41(c):** c) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

1065. I have reproduced above the single dexamethasone dose (c) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the single dexamethasone dose element of claim 41(c).

1066. Herrstedt discloses a regimen for treating chemotherapy-induced nausea and vomiting (CINV) wherein the chemotherapy is moderately emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cyclophosphamide plus an anthracycline") (citing EX1034 (Warr)). Herrstedt identifies this as "***the MEC study***" evaluating the use of aprepitant, and reports "a significant benefit in complete response of 9% was seen in the aprepitant arm (P = 0.015, response rates 50.8% versus 42.5%, respectively)." EX1010 (Herrstedt), 146. Herrstedt further discloses that the administration details are provided in the Warr (EX1034) study. EX1010 (Herrstedt), 146 (citing EX1034 (Warr)).

1067. Warr expressly confirms that the addition of an NK_1 receptor antagonist (aprepitant) to a therapeutic regimen of 5-HT_3 receptor antagonist (ondansetron) and dexamethasone provided improved treatment of CINV induced by moderately emetogenic chemotherapy. EX1034 (Warr), Abstract.

1068. Warr also describes its regimen comprises a single administration of dexamethasone without administering a second dose for a five day treatment period after chemotherapy. Warr explains that "[p]atients were randomly assigned

to either an ***aprepitant regimen*** (day 1, APR 125 mg, ondansetron (OND) 8 mg, and ***dexamethasone 12 mg*** before chemotherapy and OND 8 mg 8 hours later; days 2 through 3, APR 80 qd) or a control regimen….” EX1034 (Warr), Abstract; *see also id.*, Table 1 (reproduced below):

Table 1. Study Medication Schedule

Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
Aprepitant (n = 438)			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
Control (n = 428)			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

The study period evaluated complete response “during 120 hours after initiation of chemotherapy” (i.e., 5 days). *Id.* Thus, Warr details that “the MEC study” of Herrstedt (EX1010 (Herrstedt), 146) treatment regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after chemotherapy.

1069. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(c).

> **41(d):** d) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

1070. I have reproduced above the multiple dexamethasone dose (d) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the multiple dexamethasone dose element of claim 41(d).

1071. Herrstedt discloses its regimen is used to treat CINV induced by chemotherapy that is highly emetogenic chemotherapy (e.g., cisplatin) and said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone (i.e., having a different strength from day one) on days two, three, and four after chemotherapy. Herrstedt identifies several studies having such dosing, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, ***dexamethasone*** and placebo ***day 1*** followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, ***dexamethasone*** and aprepitant ***day 1*** followed by ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

EX1010 (Herrstedt), 146; *id*. (studies involved "patients receiving ***cisplatin-based, highly emetogenic chemotherapy***"). Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1072. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen to treat CINV induced by highly emetogenic chemotherapy comprises administering a first dose of dexamethasone on day one and a second dose (i.e., having a different strength from day one) on days two, three, and four after chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin (highly emetogenic chemotherapy), the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral ***dexamethasone 12 mg on Day 1***; oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on Days 2-3***; and oral ***dexamethasone 8 mg on Day 4***." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli explains that this NK_1 receptor antagonist regimen "provided superior antiemetic protection compared with standard therapy" without said NK_1 receptor antagonist. *Id.* Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral ***dexamethasone 12 mg*** on day 1, oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on days 2 and 3***, and oral ***dexamethasone 8 mg on day 4***." EX1037 (Hesketh), 4113. Hesketh describes this NK_1 receptor antagonist regimen "provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy." *Id.*, Abstract. Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy by administering a

first dose of dexamethasone on day one and a second dose (i.e., having a different strength from day one) on days two, three, and four after chemotherapy. As I explained above (Section XXIII.A, Claim 1), it would have been obvious to employ netupitant as the NK_1 receptor antagonist in Herrstedt's summarized studies.

1073. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(d).

> **41(e):** e) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

1074. I have reproduced above the prophylactic dose (e) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the prophylactic dose element of claim 41(e).

1075. Herrstedt discloses the NK_1 receptor antagonist and dexamethasone are administered in conjunction with the chemotherapy. Herrstedt summarizes two studies administering the triple antiemetic drug combination described above. *See* Claim 1, above; EX1010 (Herrstedt), 146. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) and employing palonosetron as the 5-HT_3 receptor antagonist (disclosed in Herrstedt) was obvious. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." *Id.* (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

1076. A POSA reviewing Herrstedt would have understood that the NK_1 receptor and dexamethasone are administered prior to administration of the chemotherapy. *See, e.g.*, EX1039 (Poli-Bigelli), 3092 (NK_1 receptor antagonist administered one hour prior to cisplatin; dexamethasone administered thirty minutes prior to cisplatin); EX1037 (Hesketh), 4113 (same). Poli-Bigelli and Hesketh both expressly confirm that the NK_1 receptor antagonist dexamethasone are administered prior to administration of the chemotherapy. Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin***, patients received either ***aprepitant*** or placebo. ***Thirty minutes prior to cisplatin***, all patients received ondansetron and ***dexamethasone***.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes this dosing regimen "provided superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin***, patients received either ***aprepitant*** or placebo. ***Thirty minutes before cisplatin***, all patients received ondansetron (infused over 15 minutes) and ***dexamethasone***.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer the NK_1 receptor antagonist and

dexamethasone prior to administration of the chemotherapy, and would have had a reasonable expectation of success that such dosing would provide relief from emesis. As I explained above, the POSA also would have had good reason to employ netupitant as the NK_1 receptor antagonist, and would have had a reasonable expectation that employing netupitant and dexamethasone prior to administration of chemotherapy would also provide the treatment of CINV (e.g., due to similar treatment profiles and mechanisms of action).

1077. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(e).

> **41(f):** f) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1078. I have reproduced above the treatment period (f) element of claim 41. It is my opinion that the combination of Herrstedt, Bös, and optionally Herrington teaches or suggests the treatment period element of claim 41(f).

1079. Herrstedt teaches or suggests each of claim elements 41(a)-41(e), as I detailed above, with Bös disclosing netupitant. Herrstedt teaches that its NK_1 receptor antagonist regimen is effective to treat CINV over a five day treatment period after chemotherapy:

> Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy or a combination of cyclophosphamide plus an anthracycline. ***Complete response, defined as "no emesis and no rescue therapy on days 1-5***

> ***postcisplatin," was the primary end-point in all studies***. Two of the HEC studies used…ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, a complete response of 72.7% in the aprepitant arm versus 53.3% in the control arm was seen[.]

EX1010 (Herrstedt), 146. Herrstedt describes the triple therapy combination is recommended "for ***prevention of acute and delayed nausea and vomiting***." *Id.*, 148 & Table 4 (MASCC guidelines). Poli-Bigelli confirms the Herrstedt regimen is effective to treat CINV for a five day period after chemotherapy. EX1039 (Poli-Bigelli), 3097 ("The addition of aprepitant…improved the control of CINV associated with highly emetogenic cisplatin-based chemotherapy in the overall study period"), *id.*, 3092 ("the overall study period (Days 1-5)"). Similarly, Hesketh confirms this. EX1037 (Hesketh), Abstract ("aprepitant was generally well tolerated and provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy"); *id.* (evaluation was of "days 1 to 5 postcisplatin").

1080. Accordingly, the combination of Herrstedt, Bös, and optionally Herrington discloses the subject matter recited in claim element 41(f).

1081. Accordingly, it is my opinion that claim 41 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

I. Claim 42

42. The method of claim 2, wherein:

a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;

b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy;

c) said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy;

d) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy;

e) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy;

f) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy;

g) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1082. Claim 42 depends from independent claim 2 and additionally recites that a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy; b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy; c) said chemotherapy comprises moderately emetogenic or highly emetogenic

chemotherapy; d) if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy; e) if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy; f) said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy; g) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

1083. As I previously addressed above, claim 2 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.B, above.

1084. Claim limitation 42(a) ("said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy") is identical to the claim limitation of claim 40. I explained above that claim 40 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.K, above. For at least the same reasons, claim limitation 42(a) was obvious over the combination of Herrstedt, Bös, and optionally Herrington.

1085. Claim limitation 42(b) ("said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof, without administering a second dose for at least five days after said chemotherapy"), claim

limitation 42(c) ("said chemotherapy comprises moderately emetogenic or highly emetogenic chemotherapy"), claim limitation 42(d) ("if said chemotherapy comprises moderately emetogenic chemotherapy, said regimen comprises a single administration of dexamethasone without administering a second dose for at least five days after said chemotherapy"), claim limitation 42(e) ("if said chemotherapy comprises highly emetogenic chemotherapy, said regimen comprises administering a first dose of dexamethasone on day one and a second dose of dexamethasone on two, three and four after said chemotherapy"), claim limitation 42(f) ("said netupitant or pharmaceutically acceptable salt thereof and said first dose of dexamethasone are administered prior to said chemotherapy"), and claim limitation 42(g) ("said regimen is effective to treat said CINV for a five day period after said chemotherapy") are each identical to claim limitations 41(a), 41(b), 41(c), 41(d), 41(e), and 41(f), respectively. I explained above that claim 41 as a whole, including each of claim limitations 41(a), 41(b), 41(c), 41(d), 41(e), and 41(f), was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.H, above. For at least the same reasons, claim limitations 42(b), 42(c), 42(d), 42(e), 42(f), and 42(g) were each obvious over the combination of Herrstedt, Bös, and optionally Herrington.

1086. Accordingly, it is my opinion that claim 42 as a whole was also obvious over Herrstedt, Bös, and optionally Herrington.

J. Motivation to Combine

1087. I provided above reasons to combine the teachings of Herrstedt and Bös. Sections XXIII.A-XXIII.C, XXIII.T. Herrstedt's studies administered 5-HT_3 receptor antagonists for multiple days but reports palonosetron has an order of magnitude greater half-life. EX1010 (Herrstedt), 146. Herrstedt similarly describes the NK_1 receptor antagonists administered for multiple days (EX1010 (Herrstedt), 146), but Bös teaches netupitant has favorable half-life and affinity characteristics (EX1014 (Bös), 19:3-10 (functional half-life of 30 hours)). The skilled artisan also would have had good reason to modify the Herrstedt triple therapy to administer the NK_1 receptor antagonist (netupitant) and 5-HT_3 receptor antagonist (palonosetron) on a single day (day one). Herrington explains there was no observed benefit in administering aprepitant on multiple consecutive days (i.e., days 1-3 of a chemotherapy treatment) as compared to administration of a single dose on only day one. EX1016 (Herrington), Abstract, 2083-2084. Herrington also teaches single administration of palonosetron only on day one. *Id.* The person having ordinary skill in the art would have understood that decreasing the number of administrations of a therapeutic lowers costs, is preferred by patients, and provides additional ease of administration. *See* Section IX.G. The POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for both provider and patient. *See, e.g.*, EX1035

(Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen…."). Thus, the POSA would have had good reason to modify the Herrstedt protocol to use the Herrington single administration in order to administer to subjects a single day dose of netupitant and palonosetron.

K. Reasonable Expectation of Success

1088. I explained above reasonable expectations of success in combining the disclosures of Herrstedt and Bös. Sections XXIII.A-XXIII.C, XXIII.U. A POSA would have had a reasonable expectation of success in achieving a therapeutically effective result by modifying Herrstedt to administer the NK_1 receptor antagonist netupitant and 5-HT_3 receptor antagonist palonosetron on a single day (prophylactically, day one of a chemotherapy treatment). Herrington's study applies a single dose of palonosetron prophylactically administered on day one prior to chemotherapy. EX1016 (Herrington), Abstract. Herrington explains the single dose of NK_1 receptor antagonist aprepitant was just as effective as multiple doses of the aprepitant, yielding similar overall therapeutic effect including anti-nausea treatment. EX1016 (Herrington), 2083-2084. Because Herrington shows similar results with a single dose of aprepitant, the POSA would have had a reasonable expectation of success in providing similar therapeutic effect with the single netupitant dose. Additionally, the POSA would have understood that single dose administration of therapeutic agents was beneficial due to convenience for

both provider and patient. *See, e.g.*, EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient ***single-day*** three-drug antiemetic regimen….").

A POSA would have had a reasonable expectation that netupitant would perform in the same manner because it was known that netupitant acted through the same mechanism to provide the same therapeutic effect and because netupitant was known to have a longer half-life. *See, e.g.*, EX1014 (Bös), 19:3-38.

1089. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and optionally Herrington to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXV. ['357 PATENT GROUND 3] '357 PATENT CLAIM 20 WAS OBVIOUS OVER HERRSTEDT, BÖS, OPTIONALLY HERRINGTON, AND OPTIONALLY ALOXI

1090. For the reasons discussed in detail below, it is my opinion that claim 20 of the '357 patent was obvious as a whole. The obviousness of claim 20 is exemplified by disclosures in the Herrstedt, Bös, optionally Herrington, and optionally Aloxi references.

1091. I have evaluated below whether the combination of Herrstedt, Bös, optionally Herrington, and optionally Aloxi discloses each and every element of claim 20 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable

expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 20

20. The method of claim 19, wherein:

a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free base.

1092. Claim 20 depends from dependent claim 19 and additionally recites a) said netupitant is administered orally as the free base in a dose of from about 200 mg to about 400 mg; and b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of from about 0.25 mg to about 0.75 mg based on the weight of the free base.

1093. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1094. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—in a range that includes from about 200 mg to about 400 mg as the free base. Bös discloses a family of NK_1 receptor antagonists including netupitant are useful for treating chemotherapy-induced emesis. EX1014 (Bös), 2:1-65, 14:9-20. Bös discloses an oral

administration dose range for its NK_1 receptor antagonists (including netupitant) that encompasses the claimed range from about 200 to about 400 mg. Bös describes:

> The effective amount for the dosage can vary within wide limits and will, of course, be fitted to the individual requirements in each particular case. In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11.

1095. Bös explicitly recognizes the application of its NK_1 receptor antagonists "for treatment induced vomiting" including "the reduction of cisplatin-induced emesis by a selective neurokinin-1-receptor antagonist." *Id.*, 1:60-64. Bös describes netupitant and its synthesis (*id.*, 14:9-15:20 (Formula Ib is netupitant)) and explains that netupitant "is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P)" (*id.*, 14:32-38). *See also id.*, 18:42-19:38 (favorable in vitro and in vivo studies as well as oral bioavailability and half-life results).

1096. It is my opinion that a POSA would have recognized Bös' range spanning two orders of magnitude (about 10 to 1,000 mg) as a favorable starting point for identifying optimal therapeutic dose amounts. It is my opinion that the

POSA would have had good reason to optimize Bös' range when determining the therapeutically effective amount of netupitant to administer to the patient, as doing so would find the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22; Section XII.A, above). Additionally, the POSA would have had a reasonable expectation of success in achieving the desired therapeutic effect orally administering that dose because Bös teaches this to be an appropriate dose for the oral administration of the family of NK_1 receptor antagonists to which netupitant belongs.

1097. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '357 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '357 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1002 ('357 patent), 7:55-61. Therefore, the '357 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based

on common factors. The POSA therefore would have found it routine to arrive at the 200-400 mg oral therapeutic dose range of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a range including from about 200 to about 400 mg when determining the amount of netupitant to orally administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

1098. Herrstedt discloses that the therapeutically effective amount (clinical dose) of palonosetron is within the range of about 0.25 to about 0.75 mg based on the weight of the free base. Herrstedt discloses, in Table 3, that it was known in the art to administer palonosetron in a 0.25 mg intravenous dose.

Table 3.

Serotonin$_3$ (5-HT$_3$)-receptor antagonists: receptor binding, metabolism via CYP450 enzymes, half-life and clinical doses.

Anti-emetic	Receptor-binding affinity pKi [–log(Ki)]	Metabolism by CYP450 enzymes				$t_{1/2}$ hours	Clinical dose mg orally/intravenously
		CYP1A1	CYP1A2	CYP2D6	CYP3A4		
Ondansetron	8.07	minor	+	+	+	4–6	16/8
Granisetron	8.42	–	–	–	+	5–8	2/1
Tropisetron	8.81	–	–	+	minor*	7–9†	5/5
Dolasetron	7.73	–	–	+	+	7	200/100
Palonosetron	10.45	–	minor	+	minor	38–40	/0.25

*This pathway is used in patients with genetic deficiencies in CYP2D6 only. †In poor metabolizers 30 hr.

EX1010 (Herrstedt), Table 3.

1099. Aloxi teaches palonosetron is administered orally as palonosetron hydrochloride in a dose of 0.5 mg based on the weight of the free base—i.e., within the range of from about 0.25 to about 0.75 mg. Aloxi teaches its palonosetron HCl is administered in capsules containing "0.56 mg of palonosetron HCl equivalent to palonosetron 0.5 mg." EX1015 (Aloxi), 3. Aloxi describes the capsules were orally

administered to patients receiving emetogenic chemotherapy to prevent CINV. *Id.*, 4. Aloxi also confirms that a POSA had good reason to select a dose from 0.25 mg to 0.75 mg of the free base of palonosetron. *See generally* Aloxi (testing 0.25 mg, 0.5 mg, and 0.75 mg palonosetron). Aloxi teaches its palonosetron HCl capsules containing 0.56 mg palonosetron HCl (corresponding with 0.5 mg of the free base) were available and approved by the FDA for treating CINV. *Id.* Aloxi thus explicitly discloses palonosetron to be administered orally as palonosetron hydrochloride in a dose squarely in the center of the claimed range from the range of 0.25 mg to 0.75 mg based on the weight of the free base.

1100. Additionally, a POSA would have had good reason to administer each of the therapeutic agents in an oral form with a reasonable expectation of success. Administration of the therapeutic agents orally was advantageous because:

> At biologically equivalent doses, oral agents are equally effective and are as safe as intravenous antiemetics. In most settings, oral agents are ***less costly and more convenient***; for those reasons, they are recommended over intravenous therapy.

EX1018 (Gralla), 2976. The POSA would have understood that oral administration is simpler, less costly, more convenient, and more preferred than intravenous administration. The POSA also would have had good reason to orally administer the Aloxi palonosetron HCl capsules because the dose and formulation described

in Aloxi had been approved by the FDA for its antinausea and antivomiting therapeutic effect. EX1015 (Aloxi), 2.

1101. Accordingly, it is my opinion that claim 20 as a whole was obvious over Herrstedt, Bös, optionally Herrington, and optionally Aloxi.

B. Motivation to Combine

1102. As I explained above (Section XXV.A), persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy to orally administer the NK_1 receptor antagonist (netupitant)—as described in Bös and as claimed—and the 5-HT_3 receptor antagonist (palonosetron) because oral administration (e.g., with a pill) was both simpler, less costly, and more convenient and more preferred than intravenous administration. *See* Section XXV.A; EX1018 (Gralla), 2976.

1103. I also explained above that the skilled artisan also would have had good reason to modify the Herrstedt triple therapy to administer the NK_1 receptor antagonist (netupitant) and 5-HT_3 receptor antagonist (palonosetron) on a single day (day one). *See* Section XXIV.J, above.

1104. The persons having ordinary skill in the art also would have been motivated to administer netupitant in a dose including from about 200 mg to about 400 mg and palonosetron hydrochloride in a dose including from about 0.25 mg to about 0.75 mg of the free base. As I explained above, these ranges were disclosed

in the prior art and the POSA would have been motivated to use the prior art ranges to determine therapeutically effective amounts for administration. Section XXV.A, above. Furthermore, Aloxi describes an FDA-approved oral capsule of palonosetron HCl that was shown to provide antiemetic effect when administered to patients receiving emetogenic chemotherapy, showing the therapeutically effective amount is 0.50 mg of palonosetron hydrochloride based on the weight of the free base. EX1015 (Aloxi), 2-4. Thus, the POSA would have had good reason to use the Aloxi capsule of palonosetron HCl in its administration of palonosetron.

C. Reasonable Expectation of Success

1105. A POSA would have had a reasonable expectation of success in achieving a therapeutically effective result by modifying Herrstedt to administer the NK_1 receptor antagonist netupitant orally. I explain above that a POSA had a reasonable expectation of success in administering netupitant and palonosetron orally in the claimed dose amounts. Section XXV.A, above; *see also* Section XXIV.K, above (reasonable expectation of success for the combination of Herrstedt, Bös, and optionally Herrington).

1106. The POSA also would have had a reasonable expectation of success in using the palonosetron HCl capsules of Aloxi to administer the Herrstedt palonosetron. Aloxi explains the orally administered palonosetron HCl capsules were as efficacious as the previously-FDA-approved intravenous formulation.

EX1015 (Aloxi), 4 (non-inferiority studies). Additionally, Aloxi provides clinical studies showing the 0.56 mg palonosetron HCl capsules were therapeutically effective in treating CINV, leading to FDA approval for prophylaxis with emetogenic chemotherapy. *Id.*, 2, 4. Therefore, the POSA would have had a reasonable expectation of success that Aloxi's palonosetron HCl capsules would treat CINV when incorporated into the Herrstedt study.

1107. Accordingly, the POSA had good reason to combine Herrstedt, Bös, optionally Herrington, and optionally Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXVI. ['357 PATENT GROUND 4] '357 PATENT CLAIM 55 WAS OBVIOUS OVER HERRSTEDT, BÖS, AND HARGREAVES

1108. For the reasons discussed in detail below, it is my opinion that claim 55 of the '357 patent was obvious as a whole. The obviousness of claim 55 is exemplified by disclosures in the Herrstedt, Bös, and Hargreaves references.

1109. I have evaluated below whether the combination of Herrstedt, Bös, and Hargreaves discloses each and every element of claim 55 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies the claim as a whole with a reasonable expectation of success. As I

explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 55

55. The method of claim 54, wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration.

1110. Claim 55 depends from dependent claim 54 and additionally recites said netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration.

1111. As I previously addressed above, claim 54 was obvious over the combination of Herrstedt and Bös. *See* Section XXIII.M, above.

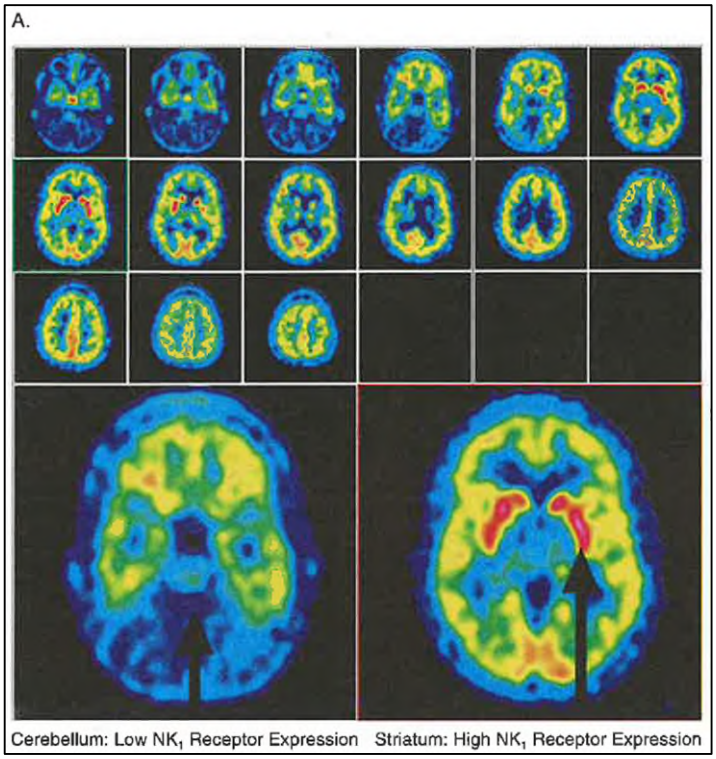
1112. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of compounds that are administered orally. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-

RQ activity was found in brain regions with high NK_1 receptor density, such as striatum….”), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

1113. Hargreaves explains that for NK_1 receptor antagonists to be therapeutically effective, they must interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 (“The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum….”), Fig. 4. Bös describes netupitant has high affinity for the NK_1 receptor antagonist (EX1014 (Bös), 18:42-48) and belongs to a family of compounds that are therapeutically effective when administered. EX1014 (Bös), 42:5-11 (“in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate”); *id.*, 18:64-19:30 (in vivo testing confirming efficacy). Hargreaves’ data demonstrate that aprepitant passes into the CNS and binds to NK_1 receptors, including in the striatum.

1114. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum.

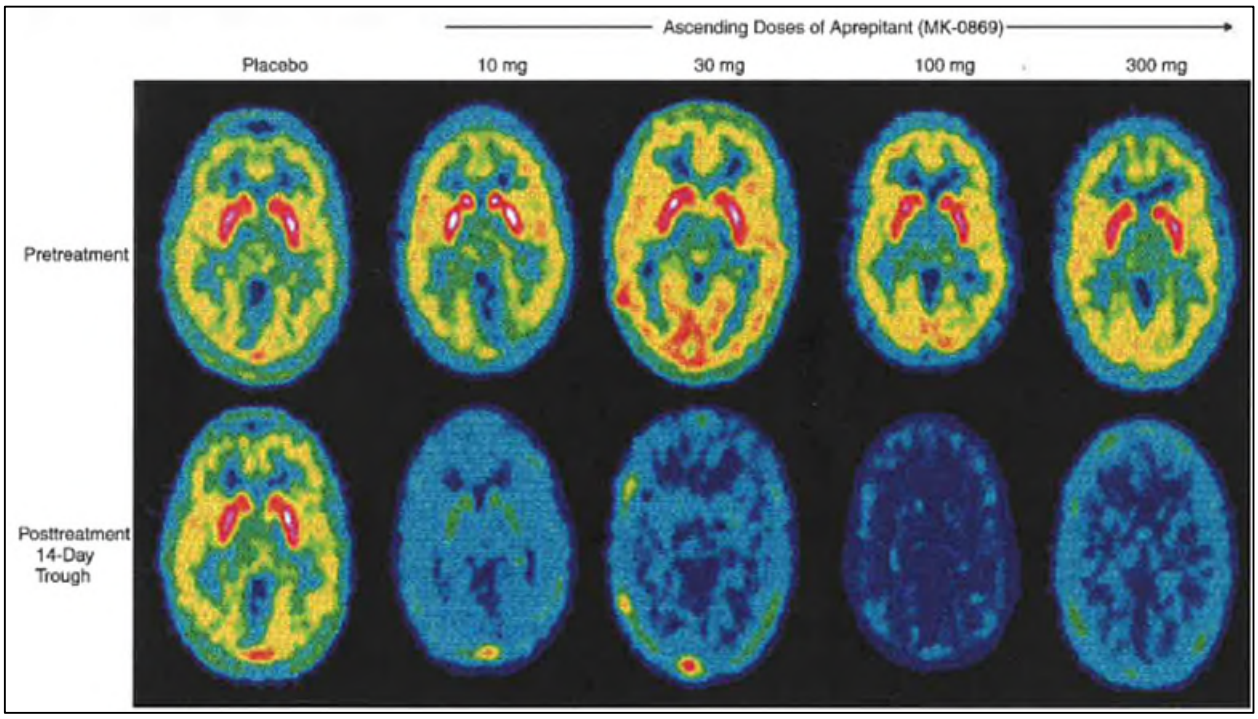
The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).

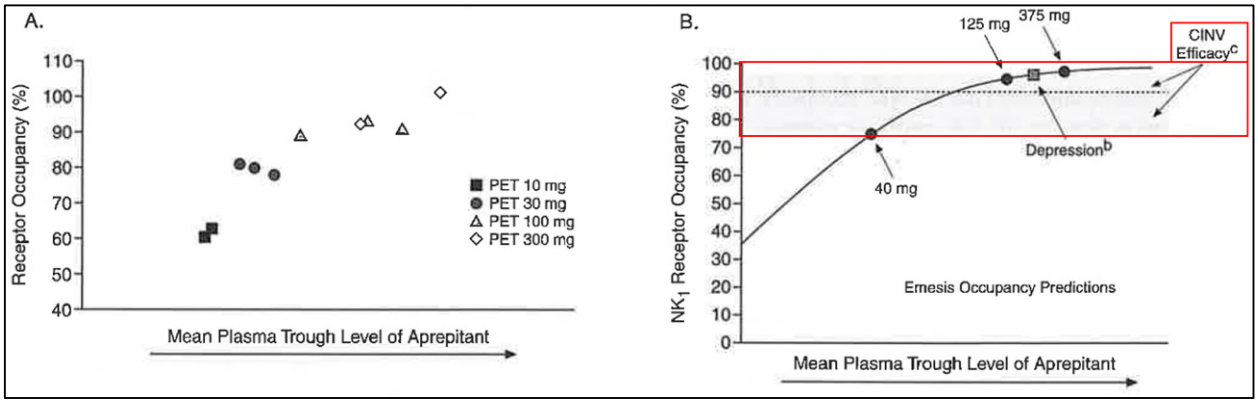


1115. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for

treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS (Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös and Hargreaves teaches or suggests netupitant occupies at least 70% of said patient's striatum NK_1 receptors after administration as recited in claim 54. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum ninety-six hours after administration would be very likely to be efficacious for treating CINV.

1116. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Section V.D, above. Furthermore, seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days (and 4 days) into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Section V.D, above. The '357 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors ***even ninety-six hours*** after administration."

EX1002 (’357 patent), 4:37-51. The patentee’s admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

1117. Accordingly, it is my opinion that claim 55 as a whole was obvious over Herrstedt, Bös, and Hargreaves.

B. Motivation to Combine

1118. I explained above why a person having ordinary skill in the art would have been motivated to combine the prior art references of Herrstedt and Bös. Section XXIII.T.

1119. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

1120. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new

5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases, and to evaluate the effect using PET imaging as described in Hargreaves.

C. Reasonable Expectation of Success

1121. I explained above why a person having ordinary skill in the art would have had a reasonable expectation of success in combining the teachings from the prior art references of Herrstedt and Bös. Section XXIII.U.

1122. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XXVI.A, above. The POSA would have understood that such studies were routinely conducted, and because the receptor occupancy being evaluated would be the same (NK_1 receptors in the striatum), it would have been routine to evaluate the effect of netupitant in the same manner described in Hargreaves.

1123. Accordingly, the POSA had good reason to combine Herrstedt, Bös, and Hargreaves to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXVII. [’357 PATENT GROUND 5] ’357 PATENT CLAIMS 24 AND 29 WERE OBVIOUS OVER HERRSTEDT, BÖS, HARGREAVES, AND OPTIONALLY HERRINGTON

1124. For the reasons discussed in detail below, it is my opinion that each of claims 24 and 29 of the ’357 patent was obvious as a whole. The obviousness of claims 24 and 29 is exemplified by disclosures in the Herrstedt, Bös, Hargreaves, and optionally Herrington references.

1125. I have evaluated below whether the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington discloses each and every element of each of claims 24 and 29 of the ’357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal “yes.”

A. Claims 24, 29

> **24.** The method of claim 19, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.
>
> **29.** The method of claim 19, wherein said netupitant occupies at least 70% of patient's striatum NK1 receptors ninety-six hours after said administration.

1126. Claims 24 and 29 are identical to one another. Claims 24 and 29 each depends from dependent claim 19 and additionally recites said netupitant occupies

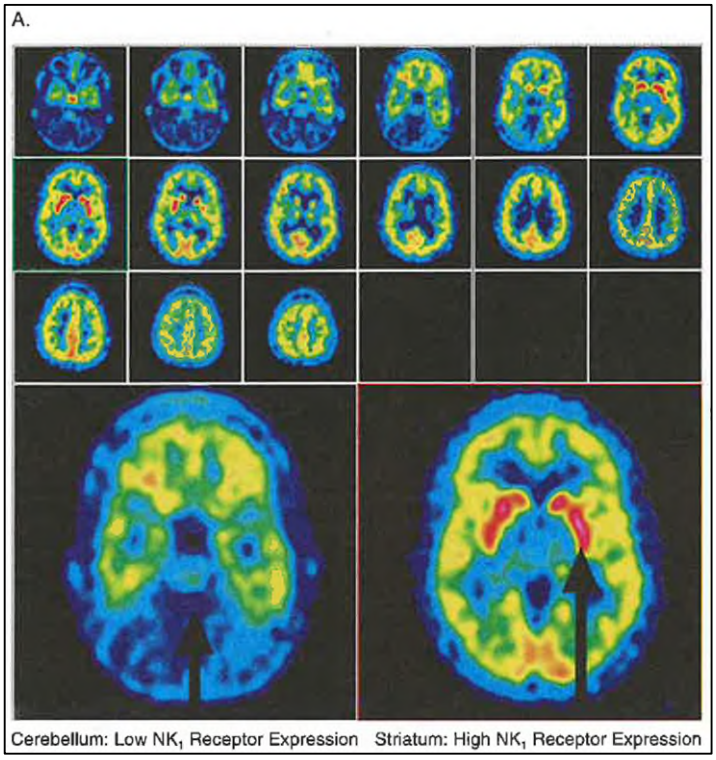
at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

1127. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1128. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of compounds that are administered orally. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

1129. Hargreaves explains that for NK_1 receptor antagonists to be therapeutically effective, they must interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. Bös describes netupitant has high affinity for the NK_1 receptor antagonist (EX1014 (Bös), 18:42-48) and belongs to a family of compounds that are therapeutically effective when administered. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"); *id.*, 18:64-19:30 (in vivo testing confirming efficacy). Hargreaves' data demonstrate that aprepitant passes into the CNS and binds to NK_1 receptors, including in the striatum.

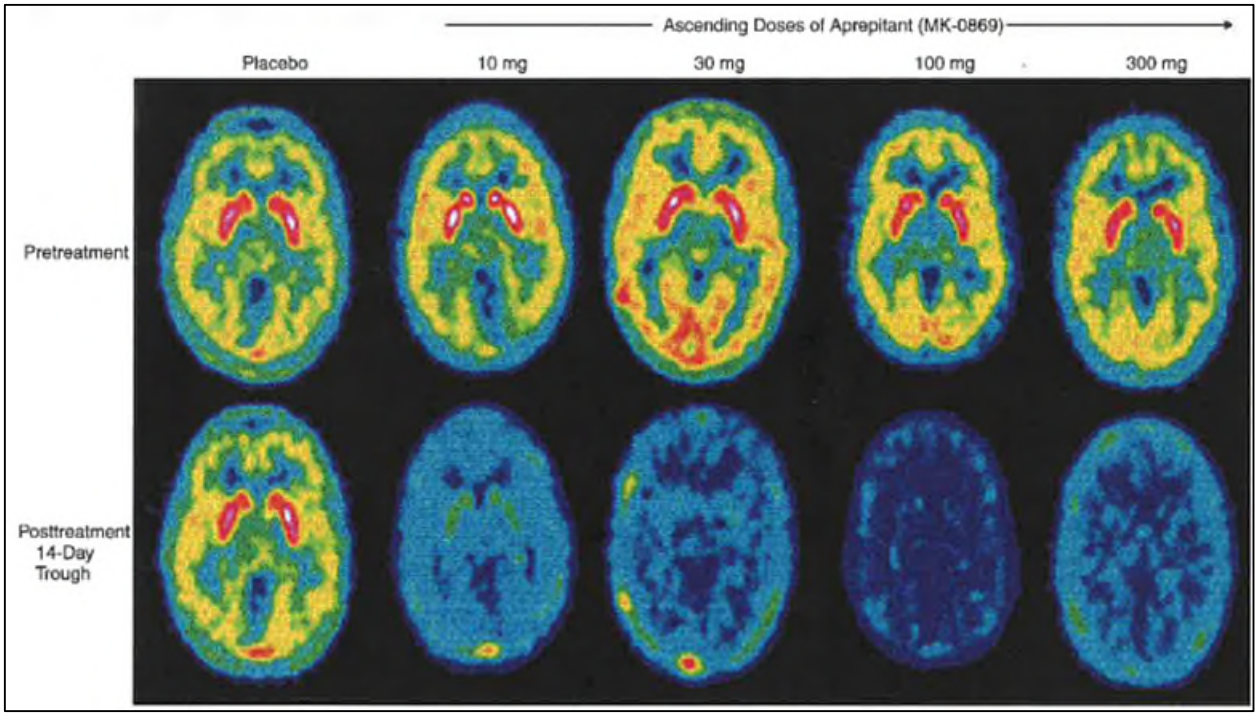
1130. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).

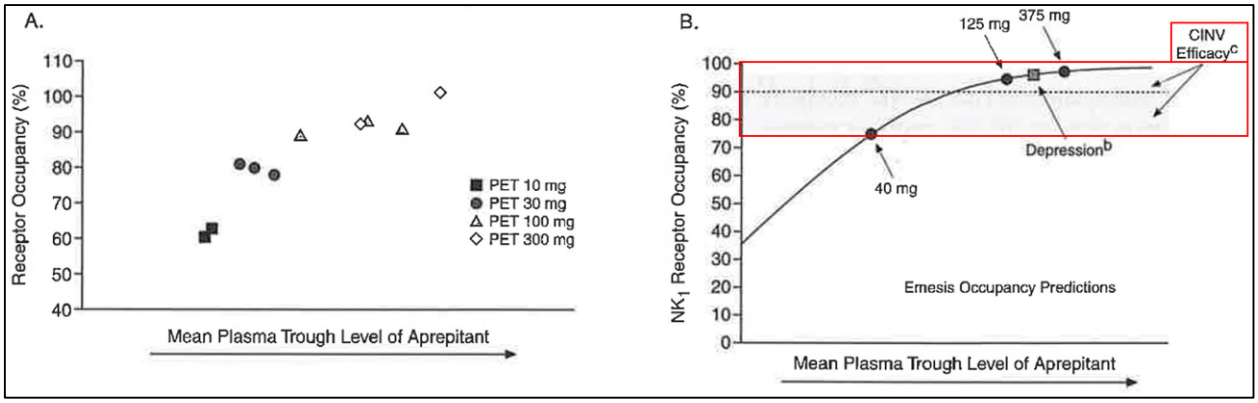


1131. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS

(Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests netupitant occupies at least 70% of said patient's striatum NK1 receptors after administration as recited in claim 18. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum ninety-six hours after administration would be very likely to be efficacious for treating CINV.

1132. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Section V.D, above. Furthermore, seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days (and 4 days) into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Section V.D, above. The '357 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors ***even ninety-six hours*** after administration."

EX1002 (’357 patent), 4:37-51. The patentee’s admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

1133. Accordingly, it is my opinion that each of claims 24 and 29 as a whole was obvious over Herrstedt, Bös, Hargreaves, and optionally Herrington.

B. Motivation to Combine

1134. I explained above why a person having ordinary skill in the art would have been motivated to combine the prior art references of Herrstedt, Bös, and optionally Herrington. Section XXIV.J.

1135. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant.

1136. Accordingly, persons having ordinary skill in the art would have had good reason to modify the Herrstedt triple active combination therapy with the new

5-HT_3 receptor antagonist (palonosetron) and Bös' NK_1 receptor antagonist (netupitant) as claimed to have an antinausea and antivomiting effect for patients receiving highly emetogenic chemotherapy during the acute and delayed phases, and to evaluate the effect using PET imaging as described in Hargreaves.

C. Reasonable Expectation of Success

1137. I explained above why a person having ordinary skill in the art would have had a reasonable expectation of success in combining the teachings from the prior art references of Herrstedt, Bös, and optionally Herrington. Section XXIV.K.

1138. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XXVII.A, above. The POSA would have understood that such studies were routinely conducted, and because the receptor occupancy being evaluated would be the same (NK_1 receptors in the striatum), it would have been routine to evaluate the effect of netupitant in the same manner described in Hargreaves.

1139. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Hargreaves, and optionally Herrington to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXVIII. ['357 PATENT GROUND 6] '357 PATENT CLAIM 28 WAS OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, AND OPTIONALLY HERRINGTON

1140. For the reasons discussed in detail below, it is my opinion that claim 28 of the '357 patent was obvious as a whole. The obviousness of claim 28 is exemplified by disclosures in the Herrstedt, Bös, Bonadeo, and optionally Herrington references.

1141. I have evaluated below whether the combination of Herrstedt, Bös, Bonadeo, and optionally Herrington discloses each and every element of claim 28 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies the claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 28

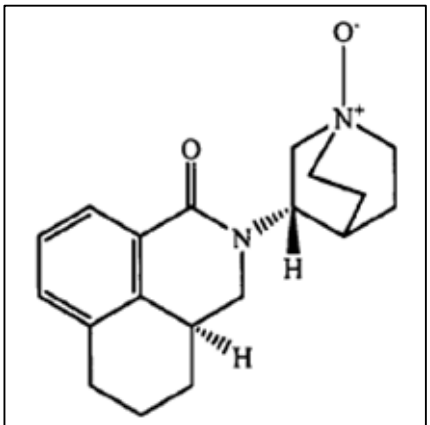
> **28.** The method of claim 19, wherein (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate is substantially absent from said palonosetron.

1142. Claim 28 depends from dependent claim 19 and additionally recites (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate is substantially absent from said palonosetron.

1143. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

1144. Before looking to evaluate whether the prior art discloses this limitation, I look to the specification of the '357 patent exclusively to understand what the claim means when it says (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate is substantially absent from said palonosetron. The '357 patent identifies (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate as a degradant of palonosetron. EX1002 ('357 patent), 5:62-6:1 ("(3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate, ***a degradation by-product of palonosetron***."). I note the '357 patent does not define an amount below which this degradant would be considered to be "substantially absent." Indeed, the only other mention of this degradant in the specification is a description of a capsule containing tablets of NK1 antagonist and, additionally, soft-gel capsules comprising palonosetron "wherein said dosage form comprises (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate in an amount that ***does not exceed 3 wt. %***." EX1002 ('357 patent), 6:11-23.

1145. Bonadeo expressly teaches the palonosetron degradant (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate is substantially absent from its palonosetron dosage form. Bonadeo identifies (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate as "Cpd1":



(3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate

Cpd1

EX1017 (Bonadeo), 11. Bonadeo details that Cpd1 "is an oxygen mediated degradation product." *Id.*, 3. Bonadeo describes its dosage form includes physical features to "enhance stability due to their protection from oxygen and oxygen mediated degradation" and that its embodiments include oral administrations of "palonosetron as palonosetron hydrochloride, wherein said palonosetron comprises ***Cpd1 in an amount of less than 1.0 wt%***." *Id.*, 3; *id.*, 4 (similar). Indeed, Bonadeo includes claims reciting a soft gelatin capsule wherein "palonosetron comprises

less than about 1 wt.% of Cpd1." *Id.*, 28 (Claim 4); *id.*, 29 (Claim 11, similar), 30 (Claim 19, "Cpd1 in an amount of less than 3.0 wt.%"). Further, Bonadeo discloses the percentage of Cpd1 is 0.5 wt% or less. EX1017 (Bonadeo), 11-12. Thus, Bonadeo discloses formulations where (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate is substantially absent.

1146. A skilled artisan would have understood Bonadeo to disclose (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate is substantially absent from its palonosetron. Bonadeo describes that, if present in its formulations, the molecule is in an amount less than 3.0 wt%, and preferably less than 1.0 wt%, and gives a specific example with 0.5 wt% or less. EX1017 (Bonadeo), 6, 9-10, 11-12 In view of the disclosure of the '357 patent—which at best discloses (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate "in an amount that does not exceed 3 wt. %" (EX1002 ('357 patent), 6:11-23)—a skilled artisan would have understood Bonadeo to provide even lower amounts of the degradant, and thus that the degradant is substantially absent from the palonosetron.

1147. A person of ordinary skill in the art would have had a reasonable expectation that Bonadeo discloses palonosetron substantially free from (3S)-3-

[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate, as further confirmed by Aloxi. Aloxi includes a list of active and inactive ingredients, neither of which list the recited claimed degradant. EX1015 (Aloxi), 3. The list of active and inactive ingredients of Aloxi match the list of active and inactive ingredients in the Bonadeo formulation. *Compare* EX1015 (Aloxi), 3 ("Each light beige opaque soft gelatin ALOXI Capsule contains 0.56 mg of palonosetron HCl equivalent to palonosetron 0.5 mg. Inactive ingredients are: mono- and di-glycerides of capryl/capric acid, glycerin, polyglyceryl oleate, water, and butylated hydroxyanisole.") *with* EX1017 (Bonadeo), Table 1 (reproduced below).

Table 1. Representative Gel-cap Formulation

Names of Ingredients	Formula (mg per capsule)		
	0.25 mg	0.50 mg	0.75 mg
Active drug substance Palonosetron HCl	0.28[a]	0.56[b]	0.84[c]
Excipients Purified water	5.57	5.57	5.57
Glycerin, anhydrous	6.40	6.40	6.40
Butylated hydroxyanisole (BHA)	0.13	0.13	0.13
Polyglyceryl oleate (Plurol Oleique CC 497)	6.65* (1.66)**	6.65* (1.66)**	6.65* (1.66)**
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	113.97* (118.96)**	113.69* (118.68)**	113.41* (118.40)**
Nitrogen	---	---	---
Theoretical fill weight	133.00 mg	133.00 mg	133.00 mg
Gelatin Capsule Shell, #3, oval (Cardinal Health)	1 capsule	1 capsule	1 capsule

[a] corresponding to 0.25 mg free base
[b] corresponding to 0.50 mg free base
[c] corresponding to 0.75 mg free base
* Formulation A (clinical batch)
** Formulation B (commercial batch)

Bonadeo reports low formation of the degradant Cpd1 with the as-formed 0.50 mg tablets. EX1017 (Bonadeo), Example 5. Bonadeo also reports the capsules were formed at commercial scale. *Id.*, Table 1 (reproduced above) ("commercial batch"). Thus a POSA would have reasonably expected that Aloxi confirms Bonadeo's palonosetron capsules are substantially free from (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate.

1148. Additionally, Aloxi identifies its palonosetron soft gelatine capsules ("gel caps") as being approved by the FDA. *Id.*, 1. A skilled artisan would have considered such FDA approval to indicate substantial absence of an impurity. The POSA would have known that to receive such FDA approval, a therapeutic would very likely require degradants to be "substantially absent." *See, e.g.*, EX1033 (FDA Q3A Impurities in New Drug Substances) (requiring identification of possible degradation products and reporting stability studies relating to the same). Thus, Aloxi confirms the palonosetron gel-caps of Bonadeo are substantially free of (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate.

1149. The '357 patent also confirms Aloxi's and Bonadeo's palonosetron gel-caps are substantially free of (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate. The '357 patent active and inactive ingredient list of its palonosetron soft-gel caps matches the

active and inactive ingredient list of the Aloxi soft-gel caps. *Compare* EX1002 (’357 patent), 14:1-26 (Table 1) *with* EX1015 (Aloxi), 3. Thus, a skilled artisan would have understood that insofar as the ’357 patent discloses a formulation of palonosetron that is substantially free of (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate, it is reasonably likely that the Aloxi formulation was also substantially free of (3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2] octan-1-olate, as discussed above.

1150. Accordingly, it is my opinion that claim 28 as a whole was obvious over Herrstedt, Bös, Bonadeo, and optionally Herrington.

B. Motivation to Combine

1151. I explained above why a person having ordinary skill in the art would have been motivated to combine the prior art references of Herrstedt, Bös, and optionally Herrington. Section XXIV.J.

1152. A POSA considering dose formulations of palonosetron would have had good reason to turn to Bonadeo for its disclosure of known degradants. The POSA formulating administrations containing palonosetron would have sought prior art identifying known degradants and would have good reason to apply known formulations that minimize said degradants as a starting point for further formulation. Bonadeo discloses known degradants including (3S)-3-[(3aS)-1-oxo-

2,3,3a,4,5,6-hexahydro-1H-benzo[de]isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate and provides formulations minimizing its formation, thus the POSA had good reason to apply the teachings of Bonadeo into the routine formulation development.

C. Reasonable Expectation of Success

1153. I explained above why a person having ordinary skill in the art would have had a reasonable expectation of success in combining the teachings from the prior art references of Herrstedt, Bös, Bonadeo, and optionally Herrington. Section XXVIII.C.

1154. The POSA would have had a reasonable expectation of applying the oral formulations of palonosetron as disclosed in Bonadeo as a starting point for further routine development. Bonadeo discloses oral formulations of palonosetron that had success in preventing degradation of known undesired degradants (EX1017 (Bonadeo), 11 (degradants), 19-22 (stability studies)) and also discloses that the formulations had been successfully administered in human subjects (EX1017 (Bonadeo), 25-26). Thus, the POSA had a reasonable expectation of success in using such formulations as a starting point for further development and in developing a formulation that similarly minimized degradant formation.

1155. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Bonadeo, and optionally Herrington to arrive at the claimed invention, and the

POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXIX. ['357 PATENT GROUND 7] '357 PATENT CLAIMS 21-23, 33-35, 37-39, 43-44, AND 46-51 WERE OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, OPTIONALLY HERRINGTON, AND OPTIONALLY ALOXI

1156. For the reasons discussed in detail below, it is my opinion that each of claims 21-23, 33-35, 37-39, 43-44, and 46-51 of the '357 patent was obvious as a whole. The obviousness of claims 21-23, 33-35, 37-39, 43-44, and 46-51 is exemplified by disclosures in the Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi references.

1157. I have evaluated below whether the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses each and every element of each of claims 21-23, 33-35, 37-39, 43-44, and 46-51 of the '357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal "yes."

A. Claim 21

21. The method of claim 19, wherein:

a) said netupitant is administered orally as the free base in a dose of about 300 mg;

b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and

c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

1158. Claim 21 depends from dependent claim 19 and additionally recites a) said netupitant is administered orally as the free base in a dose of about 300 mg; b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

1159. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

21(a): a) said netupitant is administered orally as the free base in a dose of about 300 mg;

1160. I have reproduced above the 300 mg netupitant (a) element of claim 21. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the 300 mg netupitant of element claim 21(a).

1161. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

1162. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg

to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating nausea and vomiting.

1163. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '357 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '357 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on these and other factors*** in addition to the present disclosure.

EX1002 ('357 patent), 7:55-61. Therefore, the '357 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to orally administer to the

patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

1164. The ’357 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’357 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1002 (’357 patent), 15:62-16:32) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* ’357 patent, Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 16:33-57), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study (*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the ’357 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

1165. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 21(a).

21(b): b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and

1166. I have reproduced above the 0.50 mg palonosetron (b) element of claim 21. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the 0.50 mg palonosetron element of claim 21(b).

1167. Bonadeo explicitly teaches palonosetron to be administered orally as palonosetron hydrochloride and that is administered in a dose of about 0.50 mg of palonosetron based on the weight of the free base. Bonadeo discloses gel-cap formulations of palonosetron and "describes representative formulations for a gel-cap solid oral dosage form containing 0.25, ***0.50*** and 0.75 mg. of palonosetron." EX1017 (Bonadeo), 17-18 & Table 1 (reproduced below).

Table 1. Representative Gel-cap Formulation

Names of Ingredients	Formula (mg per capsule)		
	0.25 mg	0.50 mg	0.75 mg
Active drug substance			
Palonosetron HCl	0.28[a]	0.56[b]	0.84[c]
Excipients			
Purified water	5.57	5.57	5.57
Glycerin, anhydrous	6.40	6.40	6.40
Butylated hydroxyanisole (BHA)	0.13	0.13	0.13
Polyglyceryl oleate (Plurol Oleique CC 497)	6.65* (1.66)**	6.65* (1.66)**	6.65* (1.66)**
Mono- and di-glycerides of Capryl/Capric Acid (Capmul MCM)	113.97* (118.96)**	113.69* (118.68)**	113.41* (118.40)**
Nitrogen	---	---	---
Theoretical fill weight	133.00 mg	133.00 mg	133.00 mg
Gelatin Capsule Shell, #3, oval (Cardinal Health)	1 capsule	1 capsule	1 capsule

[a] corresponding to 0.25 mg free base
[b] corresponding to 0.50 mg free base
[c] corresponding to 0.75 mg free base
* Formulation A (clinical batch)
** Formulation B (commercial batch)

Bonadeo describes its 0.50 mg soft-gel capsules of palonosetron was administered orally to subjects. *Id.*, 26 (Example 13). Bonadeo also describes the oral soft-gel capsules as including palonosetron hydrochloride as an active ingredient (*see, e.g.*, *id.*, Table 1, above) and that the dose of palonosetron was 0.50 mg based on the weight of the free base (*id.*).

1168. Aloxi also discloses palonosetron is administered orally as palonosetron hydrochloride and that it is administered in a dose of about 0.56 mg of palonosetron hydrochloride, corresponding to about 0.50 mg of palonosetron based on the weight of the free base. Aloxi capsules contained 0.56 mg palonosetron HCl (corresponding to 0.5 mg of palonosetron free base) formulated for oral administration and indicated for the prevention of acute nausea and vomiting following initial and repeat courses of moderately emetogenic chemotherapy. EX1015 (Aloxi), 1-4; *id.*, 3 ("Each light beige opaque soft gelatin ALOXI Capsule contains 0.56 mg of ***palonosetron HCl equivalent to palonosetron 0.5 mg***."). A POSA would have had good reason to use the FDA approved palonosetron HCl dose (0.56 mg) as the therapeutically effective amount of palonosetron administered to the patient. The POSA also would have had a reasonable expectation of success in achieving the desired therapeutic result by administering this known and approved therapeutic amount because the specific dose had gone through the rigors of FDA approval.

1169. I also note that the ’357 patent itself does not ascribe any particular or unexpected results associated with the 0.56 mg dose of palonosetron hydrochloride. I have reviewed the ’357 patent and do not observe any particular benefits linked with a 0.56 mg dose of palonosetron HCl specifically. For example, the specification explains that 0.5 mg of palonosetron was selected for inclusion into a formulation, and that the 0.56 mg of palonosetron corresponded with 0.5 mg free base, but does not explain this dose of palonosetron to be better than any others. EX1002 (’357 patent), 13:56-14:26. Therefore, based on my review of the ’357 patent, there is no particular or unexpected benefit ascribed specifically to the 0.50 mg dose of palonosetron based on the weight of the free base.

1170. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 21(b).

> **21(c):** c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

1171. I have reproduced above the single unit dosage form (c) element of claim 21. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the single unit dosage form element of claim 21(c).

1172. Herrstedt teaches an effective amount of the antiemetic regimen is administered in conjunction with administering the chemotherapy. Herrstedt

provides a summary of two studies employing the triple anti-emetic drug regimen described above. *See* Claim 1. As discussed above for claim 1, employing netupitant as the NK_1 receptor antagonist (disclosed in Bös) and employing palonosetron as the 5-HT_3 receptor (disclosed in Herrstedt) with dexamethasone was an obvious anti-emetic regimen. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in "the Hesketh study." EX1010 (Herrstedt), 146 (citing EX1039 (Poli-Bigelli); EX1037 (Hesketh)).

1173. A POSA reviewing Herrstedt would have understood that an effective amount of the 5-HT_3 and NK_1 receptor antagonists is prophylactically administered less than 2 hours prior to chemotherapy. For example, Poli-Bigelli and Hesketh each expressly confirms that the antiemetic combination (NK_1 and 5-HT_3 receptor antagonists with dexamethasone) of Herrstedt is administered prior to the emetogenic chemotherapy (e.g., cisplatin). Poli-Bigelli describes, with regard to its timing:

> ***One hour prior to cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes prior to cisplatin***, all patients received ***ondansetron and dexamethasone***.

EX1039 (Poli-Bigelli), 3092. Poli-Bigelli describes that dosing the NK_1 receptor antagonist (aprepitant) and the 5-HT_3 receptor antagonist (ondansetron) with dexamethasone prior to the emetogenic chemotherapy (cisplatin) "provided

superior antiemetic protection compared with standard therapy alone and was generally well tolerated." *Id.*, Abstract. Similarly, Hesketh describes, with regard to its timing:

> ***One hour before cisplatin,*** patients received either ***aprepitant*** or placebo. ***Thirty minutes before cisplatin***, all patients received ***ondansetron*** (infused over 15 minutes) ***and dexamethasone***.

EX1037 (Hesketh), 4113. Hesketh also praised the aprepitant triple drug combination as "superior to standard therapy overall." *Id.*, 4115. Thus, a POSA would have had good reason to administer the therapeutically effective amount of the antiemetic drug combination within one hour of chemotherapy (i.e., less than 2 hours prior to chemotherapy), and would have had a reasonable expectation of success that such dosing would provide relief from emesis. Thus, it was obvious that netupitant and palonosetron are administered less than 2 hours prior to said chemotherapy.

1174. Herrington's studies concomitantly administer the 5-HT_3 and NK_1 receptor antagonists shortly before administration of chemotherapy, as I described above. Bonadeo discloses "solid oral dosage forms of palonosetron hydrochloride" and describes a preferable form of administration is "liquid filled capsules." EX1017 (Bonadeo), Abstract. Bonadeo suggests its oral formulations of palonosetron include at least a second active ingredient—i.e., is a single unit dosage form containing palonosetron and another active ingredient. For example,

Bonadeo describes that "[u]pon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the ***pharmaceutical actives*** from the liquid core into the body." EX1017 (Bonadeo), 16. Additionally, Bonadeo pronounces that, throughout its disclosure, "reference to 'an active pharmaceutical agent' includes ***more than one active pharmaceutical agent***." *Id.*, 5.

1175. A person of ordinary skill in the art would have good reason to formulate netupitant and palonosetron together into a fixed combination (a single unit dosage form). As summarized by Herrstedt, and as disclosed by Poli-Bigelli and Hesketh, 5-HT_3 receptor antagonists such as palonosetron are administered shortly after administration of NK_1 receptor antagonists, such as netupitant. EX1039 (Poli-Bigelli), 3092; EX1037 (Hesketh), 4113. Where multiple drugs are administered in constant dosages (as with the antiemetic combination therapy of Herrstedt) and where they are administered in close proximity to one another (as with the antiemetic combination therapy of Herrstedt), "there are considerable practical advantages in giving the required drugs in single formulation." EX1061 (Cromie), 78. A person of ordinary skill in the art would have recognized that administering a single unit dosage form containing palonosetron and netupitant would "give greater convenience and safety for patient and doctor and reduce the risk of errors in medication." *Id.* The POSA would have understood that any

potential disadvantages of fixed dose administration were outweighed by the advantages. *Id.*, 80-85. Since all participants in the studies summarized by Herrstedt received the same dose amounts of netupitant and palonosetron (i.e., the drugs are administered in constant dosages) and are administered in close proximity to one another (approximately 30 minutes), the POSA would have had good reason to formulate a single unit dose with both palonosetron and netupitant.

1176. A skilled artisan would have had a reasonable expectation of successfully formulating a single unit dose with palonosetron and netupitant. It was well within the artisan's knowledge and skill set to develop formulations containing two active pharmaceutical ingredients, as described by Bonadeo, above. For example, it was known to develop capsules that include multiple therapies, such as a capsule-inside-a-capsule wherein the active pharmaceutical ingredients are administered together but kept physically separate from one another. Sanso describes, for example:

> A pharmaceutical dosage form particularly suitable for the administration of active principles in multiple therapies is disclosed. The pharmaceutical dosage form is a ***double capsule*** where in an internal capsule is placed inside an external one. ***Each internal and external capsule includes one or more active principles***.

EX1060 (Sanso), Abstract. Sanso explains that numerous prior art references disclose the use of such double capsules, and that it was within the skilled

artisan's ability to adjust the capsule materials to provide desired characteristics for delivery of each medication. *Id.*, 1:48-2:8. Indeed, it was known that the capsules for making such double capsule delivery systems were "already on the market" and available for purchase. *Id.*, 3:57-4:42.

1177. Additionally, the POSA would have had good reason to turn to the dose administration of Bonadeo when developing a fixed combination dose of palonosetron and netupitant because Bonadeo explains its favorable use in developing a palonosetron capsule. Bonadeo discloses "capsules of palonosetron have been developed that exhibit excellent bioavailability when orally ingested, and stability when stored for prolonged periods of time." EX1017 (Bonadeo), 2. Bonadeo states that "an oral delivery option for palonosetron, especially in solid form, would be particularly attractive" because "it is generally recognized that injection drug delivery systems prevent special problems with respect to storage life and stability of the active ingredient [and they] are also inconvenient when self administered and have increased risk of contamination and human error." *Id.* Thus, Bonadeo teaches oral formulations of palonosetron, such as those administered in capsules, are preferable to intravenous administration. *See also id.*, 3 ("Dosage forms of palonosetron, including methods of manufacture, have also been developed with enhanced stability due to their protection from oxygen and oxygen mediated degradation.").

1178. Thus, a person of ordinary skill in the art would have had good reason to formulate netupitant and palonosetron together in a single fixed dose form (i.e., a single unit dosage form) and administer the dose prophylactically—less than 2 hours prior to chemotherapy.

1179. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 21(c).

1180. Accordingly, it is my opinion that claim 21 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

B. Claim 22

22. The method of claim 19, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

1181. Claim 22 depends from dependent claim 19 and additionally recites a) said chemotherapy comprises moderately emetogenic chemotherapy; b) said netupitant is administered orally as the free base in a dose of about 300 mg; c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

1182. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

> **22(a):** a) said chemotherapy comprises moderately emetogenic chemotherapy;

1183. I have reproduced above the moderately emetogenic (a) element of claim 22. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the moderately emetogenic element of claim 22(a).

1184. Herrstedt suggests the chemotherapy is moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately

emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

1185. Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the CINV induced by moderately emetogenic chemotherapy. Herrstedt describes its antiemetic therapy is applicable for treating CINV induced by said moderately emetogenic chemotherapy. Herrstedt discloses its NK_1 antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract.

1186. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 22(a).

> **22(b):** b) said netupitant is administered orally as the free base in a dose of about 300 mg;
>
> **22(c):** c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;
>
> **22(d):** d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; and

1187. I have reproduced above elements (b), (c), and (d) of claim 22. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the each of elements 22(b), 22(c), and 22(d) of claim 22.

1188. Claim limitation 22(b) ("said netupitant is administered orally as the free base in a dose of about 300 mg"), claim limitation 22(c) ("said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base"), and claim limitation 22(d) ("said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy") are each identical to claim limitations 21(a), 21(b), and 21(c), respectively (except that the "single unit dosage" of claim limitation 21(c) is referred to as a "combination unit dosage" in claim limitation 22(d)). I explained above that claim 21 as a whole, including each of claim limitations 21(a), 21(b), and 21(c) was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.A, above. For at least the same reasons, claim limitations 22(b), 22(c), and 22(d) were each obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

1189. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim elements 22(b), 22(c), and 22(d).

> **22(e):** e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy.

1190. I have reproduced above the dexamethasone administration (e) element of claim 22. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the dexamethasone administration element of claim 22(e).

1191. Herrstedt summarizes that, in a study treating CINV induced by moderately emetogenic chemotherapy, the antiemetic combination therapy was tested and showed "a significant benefit." EX1010 (Herrstedt), 146. Herrstedt further discloses that the administration details are provided in the underlying study (EX1034 (Warr)). *Id.* Warr expressly confirms that the addition of an NK_1 receptor antagonist (aprepitant) to a therapeutic regimen of 5-HT_3 receptor antagonist (ondansetron) and dexamethasone provided improved treatment of CINV induced by moderately emetogenic chemotherapy. EX1034 (Warr), Abstract.

1192. Warr also describes its dexamethasone is administered in a dose of about 12 mg less than 2 hours prior to chemotherapy. Warr explains that "[p]atients were randomly assigned to either an aprepitant regimen (day 1, APR 125 mg, ondansetron (OND) 8 mg, and ***dexamethasone 12 mg before chemotherapy*** and OND 8 mg 8 hours later; days 2 through 3, APR 80 qd) or a control regimen…." EX1034 (Warr), Abstract. This dose regimen is confirmed by Warr Table 1, which also confirms that the 12 mg of dexamethasone is

administered 30 minutes prior to chemotherapy (i.e., less than 2 hours prior to chemotherapy). *Id.*, Table 1 (reproduced below):

Table 1. Study Medication Schedule

Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
Aprepitant (n = 438)			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
Control (n = 428)			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

Thus, Warr details that "the MEC study" of Herrstedt (EX1010 (Herrstedt), 146) treatment regimen includes dexamethasone administered in a dose of about 12 mg less than 2 hours prior to chemotherapy.

1193. Warr describes its dexamethasone is administered in a dosage form independent of the other medications. EX1034 (Warr), Abstract & Table 1 (above). Thus, Warr details that "the MEC study" of Herrstedt (EX1010 (Herrstedt), 146) treatment regimen includes dexamethasone administered in a dosage form independent from the 5-HT_3 and NK_1 receptor antagonists.

1194. A POSA would have been motivated, when developing the fixed dose unit dosage form containing palonosetron and netupitant, to keep dexamethasone in a dosage form independent of said combination unit dosage form. As I explained above (Section XXIX.A, claim element 21(c)), it was known that when multiple "drugs are used at ***constant dosage***" they may be administered together in a single

dosage form. EX1061 (Cromie), 78. Indeed, Cromie indicates that "drugs [] administered at ***constant dosage***" is a prerequisite for a POSA to experience the "considerable practical advantages in giving the required drugs in single formulation." *Id.* In contrast, a POSA would have known that dexamethasone ***is not administered in a constant dosage***. For example, in Herrstedt's triple antiemetic therapy, dexamethasone is administered in a 12 mg dose on the first day for treating moderately emetogenic chemotherapy (EX1034 (Warr), Abstract, Table 1) but is administered in both 12 mg (day one) and 8 mg (days two-four) doses for treating highly emetogenic chemotherapy. EX1039 (Poli-Bigelli), Abstract; EX1037 (Hesketh), 4113. Thus, because dexamethasone is not administered at a constant dosage and varies depending on the emetogenic event, a POSA would have formulated the unit dosage form to include palonosetron and netupitant but would not include dexamethasone. It was obvious to administer the dose of dexamethasone in a dosage form independent of the combination unit dosage form.

1195. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 22(e).

1196. Accordingly, it is my opinion that claim 22 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

C. Claim 23

23. The method of claim 19, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg;

c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;

d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy;

e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and

f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

1197. Claim 23 depends from dependent claim 19 and additionally recites a) said chemotherapy comprises highly emetogenic chemotherapy; b) said netupitant is administered orally as the free base in a dose of about 300 mg; c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy; e) said dexamethasone is administered in a dose of

about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

1198. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIV.B, above.

23(a): a) said chemotherapy comprises highly emetogenic chemotherapy;

1199. I have reproduced above the highly emetogenic (a) element of claim 23. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the highly emetogenic element of claim 23(a).

1200. Herrstedt discloses its regimen is used to treat CINV induced by chemotherapy that is highly emetogenic chemotherapy (e.g., cisplatin). Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2–4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2–4 plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection

days 2–4.

EX1010 (Herrstedt), 146; *id.* (studies involved "patients receiving ***cisplatin-based, highly emetogenic chemotherapy***"). Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1201. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen treats CINV induced by highly emetogenic chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin (highly emetogenic chemotherapy), the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg on Day 1; oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on Days 2-3; and oral dexamethasone 8 mg on Day 4." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli explains that this NK_1 receptor antagonist regimen "provided superior antiemetic protection compared with standard therapy" without said NK_1 receptor antagonist. *Id.* Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4." EX1037 (Hesketh), 4113. Hesketh describes this NK_1 receptor antagonist regimen "provided consistently superior protection against CINV in patients receiving

highly emetogenic cisplatin-based chemotherapy." *Id.*, Abstract. Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy.

1202. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 23(a).

> **23(b):** b) said netupitant is administered orally as the free base in a dose of about 300 mg;
>
> **23(c):** c) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base;
>
> **23(d):** d) said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy;

1203. I have reproduced above elements (b), (c), and (d) of claim 23. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the each of elements 23(b), 23(c), and 23(d) of claim 23.

1204. Claim limitation 23(b) ("said netupitant is administered orally as the free base in a dose of about 300 mg"), claim limitation 23(c) ("said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base"), and claim limitation 23(d) ("said netupitant and palonosetron are administered as a combination unit dosage form less than 2 hours prior to said chemotherapy") are each identical to claim limitations 22(b),

22(c), and 22(d), respectively. I explained above that claim 22 as a whole, including each of claim limitations 22(b), 22(c), and 22(d), was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.B, above. For at least the same reasons, claim limitations 22(b), 22(c), and 22(d) were each obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

1205. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim elements 22(b), 22(c), and 22(d).

> **23(e):** e) said dexamethasone is administered in a dose of about 12 mg, in a dosage form independent of said combination unit dosage form, less than 2 hours prior to said chemotherapy; and

1206. I have reproduced above the initial dexamethasone (e) element of claim 23. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the initial dexamethasone element of claim 23(e).

1207. Herrstedt discloses its regimen treating CINV induced by highly emetogenic chemotherapy includes prophylactically administered dexamethasone prior to chemotherapy. Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, ***dexamethasone*** and placebo ***day 1*** followed by dexamethasone plus placebo days 2–4 with

> ondansetron, ***dexamethasone*** and aprepitant ***day 1*** followed by dexamethasone days 2–4 plus aprepitant days 2–3…. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1208. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen includes dexamethasone administered in a dose of about 12 mg less than 2 hours prior to chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin, the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and ***oral dexamethasone 12 mg on Day 1***." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli also explains that "***[t]hirty minutes prior to cisplatin***, all patients received ondansetron and dexamethasone." *Id.*, 3092. Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral ***dexamethasone 12 mg on day 1***." EX1037 (Hesketh), 4113. Hesketh also explains that "***[t]hirty minutes before cisplatin***, all patients received ondansetron (infused over 15 minutes) and ***dexamethasone***." Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by

highly emetogenic chemotherapy and that those studies administered dexamethasone in a dose of about 12 mg less than 2 hours prior to chemotherapy.

1209. A POSA would have been motivated, when developing the fixed dose unit dosage form containing palonosetron and netupitant, to keep dexamethasone in a dosage form independent of said combination unit dosage form. As I explained above (Section XXIX.A, claim element 21(c)), it was known that when multiple "drugs are used at ***constant dosage***" they may be administered together in a single dosage form. EX1061 (Cromie), 78. Indeed, Cromie indicates that "drugs [] administered at ***constant dosage***" is a prerequisite for a POSA to experience the "considerable practical advantages in giving the required drugs in single formulation." *Id.* In contrast, a POSA would have known that dexamethasone ***is not administered in a constant dosage***. For example, in Herrstedt's triple antiemetic therapy, dexamethasone is administered in a 12 mg dose on the first day for treating moderately emetogenic chemotherapy (EX1034 (Warr), Abstract, Table 1) but is administered in both 12 mg (day one) and 8 mg (days two-four) doses for treating highly emetogenic chemotherapy. EX1039 (Poli-Bigelli), Abstract; EX1037 (Hesketh), 4113. Thus, because dexamethasone is not administered at a constant dosage and varies depending on the emetogenic event, a POSA would have formulated the unit dosage form to include palonosetron and netupitant but would not include dexamethasone. It was obvious to administer the

dose of dexamethasone in a dosage form independent of the combination unit dosage form.

1210. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 23(e).

> **23(f):** f) said dexamethasone is further administered in a dose of about 8 mg on days 2, 3 and 4 following said chemotherapy.

1211. I have reproduced above the subsequent dexamethasone (f) element of claim 23. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the subsequent dexamethasone element of claim 23(f).

1212. Herrstedt discloses its regimen treating CINV induced by chemotherapy includes dexamethasone administered on days 2, 3 and 4 following chemotherapy. Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, dexamethasone and aprepitant day 1 followed by ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

EX1010 (Herrstedt) further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1213. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen includes dexamethasone administered in a dose of about 8 mg on days 2, 3 and 4 following chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin, the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg on Day 1; oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on Days 2-3***; and oral ***dexamethasone 8 mg on Day 4***." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli explains that this regimen "provided superior antiemetic protection compared with standard therapy" without an NK_1 receptor antagonist. *Id.* Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on days 2 and 3***, and oral ***dexamethasone 8 mg on day 4***." EX1037 (Hesketh), 4113. Hesketh describes this regimen "provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy." *Id.*, Abstract. Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy and that those studies

administered dexamethasone in a dose of about 8 mg on days 2, 3 and 4 following chemotherapy.

1214. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 23(f).

1215. Accordingly, it is my opinion that claim 23 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

D. Claim 33

33. The method of claim 21, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1216. Claim 33 depends from dependent claim 21 and additionally recites a) said chemotherapy is highly emetogenic chemotherapy; and b) said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1217. As I previously addressed above, claim 21 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.A, above.

1218. Herrstedt discloses a method for preventing "[c]hemotherapy-induced nausea and vomiting" (CINV) in a subject receiving highly emetogenic cancer

chemotherapy by administering an antiemetic drug combination. EX1010 (Herrstedt), 143; *id.*, 144 ("Most anti-emetic agents act by binding at one of these receptors (antagonist), thereby preventing the (agonist) effect of the transmitters released, following administration of cancer chemotherapy."), 146. Herrstedt describes administering its combination therapy to prevent nausea and vomiting "in patients receiving ***cisplatin***-based, ***highly emetogenic chemotherapy***." *Id.*, 146.

1219. Herrstedt describes treating CINV during the acute and delayed phases of chemotherapy. Herrstedt explains its triple combination antiemetic improves efficacy "against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Herrstedt describes studies treating nausea and vomiting with a triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1220. Poli-Bigelli expressly confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of CINV induced by highly emetogenic chemotherapy (cisplatin). EX1039 (Poli-Bigelli), 3096-3097.

For example, Poli-Bigelli describes prevention of nausea via improvement of complete response over periods including the acute and delayed phases, and also explains this parameter is a stand-in for the control of nausea:

> In the assessments of complete response over specific periods after cisplatin, the aprepitant regimen provided a ***substantial improvement*** of 14 percentage points over standard therapy in the prevention of ***acute*** symptoms, and a ***highly remarkable improvement*** of about 21 percentage points in the prevention of ***delayed*** CINV.
>
> Because patients were considered treatment failures if they either vomited or took rescue medication to alleviate nausea, ***the complete response endpoint*** not only reflects control of emesis but also indirectly reflects control of nausea.

EX1039 (Poli-Bigelli), 3096. Thus, Poli-Bigelli identified the addition of NK_1 receptor antagonist (aprepitant) as disclosed in Herrstedt's triple therapy combination was effective to treat CINV during the acute phase of CINV, and especially during the delayed phase of chemotherapy induced nausea and vomiting.

1221. Hesketh also confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1037 (Hesketh), 4116-4117. As with Poli-Bigelli, Hesketh explains that Herrstedt's triple therapy combination improved complete response during both acute and delayed phases and that this directly indicated prevention of nausea:

> [T]he addition of a 3-day regimen of aprepitant significantly ***improved complete response*** as compared with standard therapy ***throughout the acute and delayed phases***. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant) was clearly ***both statistically significant and clinically meaningful***, and was particularly marked during the delayed phase.

EX1037 (Hesketh), 4117. Regarding said complete response parameter, "[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (85.4% v 55.8%***; P < .001)." *Id.*, 4115; *see also id.*, Figure 2 (reproduced below).

1222. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen

was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

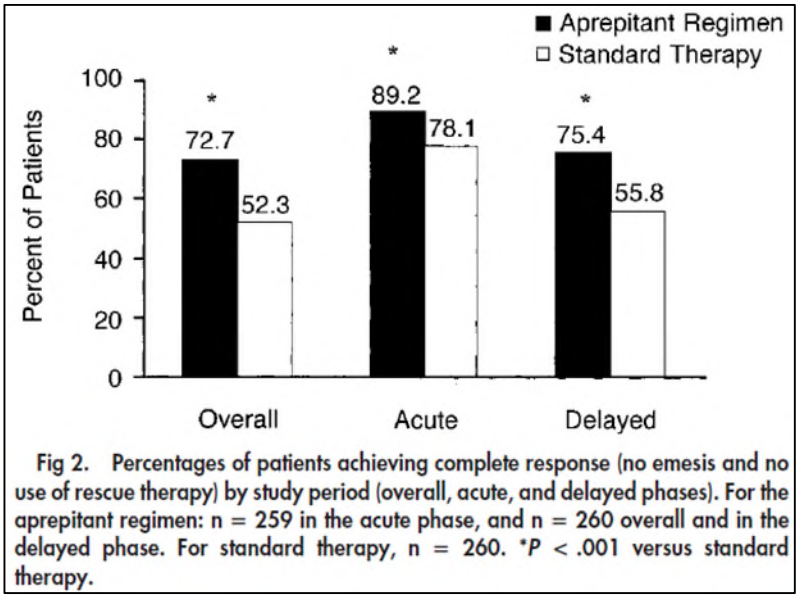


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *P < .001 versus standard therapy.

A POSA would therefore have understood, based on Hesketh's complete response results, that administration of Herrstedt's triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV. Indeed, Hesketh explains that Herrstedt's triple therapy combination ("aprepitant group") was overall superior to the standard therapy (without aprepitant):

> Regardless of the specific end point, ***response rates overall and in the acute and delayed phases were consistently greater*** for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and ***complete protection*** (which

> ***incorporates both emesis and nausea assessment***), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were ***consistently numerically higher in the aprepitant group***. The higher response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, ***indicate that aprepitant provided some benefit against nausea as well as emesis***.

EX1037 (Hesketh), 4117. Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that administration of the triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV.

1223. Accordingly, it is my opinion that claim 33 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

E. Claim 34

34. The method of claim 21, wherein:

a) said chemotherapy is highly emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1224. Claim 34 depends from dependent claim 21 and additionally recites a) said chemotherapy is highly emetogenic chemotherapy; and b) said regimen is

effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1225. As I previously addressed above, claim 21 was obvious over the combination of Herrstedt, Bös, and optionally Herrington. *See* Section XXIX.A, above.

1226. Herrstedt discloses a regimen for treating chemotherapy-induced nausea and vomiting (CINV) wherein the chemotherapy is highly emetogenic chemotherapy. EX1010 (Herrstedt), 146 ("cisplatin-based, highly emetogenic chemotherapy"). Herrstedt discloses its NK_1 antiemetic combination provides therapeutic effect for "emesis induced by highly or moderately emetogenic chemotherapy" noting in particular that the NK_1 receptor antagonist is "also active in the protection against delayed emesis." *Id.*, Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1227. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was used to treat nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy, and the regimen is effective to prevent nausea or reduce the severity of nausea in patients during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which

Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the

complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of Herrstedt treats nausea and vomiting where the emesis inducing event is highly emetogenic chemotherapy (i.e., cisplatin) and is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

1228. Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, the

palonosetron of Herrstedt, and would have had a reasonable expectation of success that such dosing would treat CINV wherein the chemotherapy is highly emetogenic chemotherapy (e.g., cisplatin) and the regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases of CINV.

1229. Accordingly, it is my opinion that claim 34 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

F. Claim 35

35. The method of claim 21, wherein:

a) said chemotherapy is moderately emetogenic chemotherapy; and

b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1230. Claim 35 depends from dependent claim 21 and additionally recites a) said chemotherapy is moderately emetogenic chemotherapy; and b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

1231. As I previously addressed above, claim 19 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.A, above.

1232. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately

emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***"). Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the chemotherapy is highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating CINV in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to effectively treat CINV where the chemotherapy is moderately emetogenic chemotherapy.

1233. Herrstedt discloses its NK_1 antiemetic regimen is effective to treat "***acute emesis*** induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1234. A POSA reviewing Herrstedt would have understood that the antiemetic regimen is effective to prevent nausea or reduce the severity of nausea during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," which Herrstedt explains is the combination of both ***acute and delayed phases*** following chemotherapy. EX1010 (Herrstedt), 146; *id.* ("Complete response, defined as 'no emesis and no rescue therapy on days 1-5 postcisplatin', was the primary end-point in all studies."). A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Poli-Bigelli expressly confirms the antiemetic dosing

regimen treats of nausea and vomiting in response to emetogenic chemotherapy during ***both*** the acute phase ***and*** the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "a highly remarkable improvement of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent nausea or reduce the severity of nausea during the acute and delayed phases. Hesketh also confirms the antiemetic dosing combination of

Herrstedt treats nausea and vomiting where the emesis inducing event is chemotherapy and the regimen is effective to prevent or reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

1235. Each of Poli-Bigelli and Hesketh describe the NK1 receptor antagonist dosing regimen is useful for preventing or reducing the severity of nausea where chemotherapy is cisplatin (highly emetogenic chemotherapy). Nonetheless, a POSA would have reasonably expected similar anti-nausea effect for treatment of nausea where the chemotherapy is moderately emetogenic because the mechanism of treatment is the same (e.g., occupancy of NK_1 and 5-HT_3 receptors). Herrstedt confirms that its regimen is applicable for treating both highly emetogenic and moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract.

1236. Therefore, a POSA would have had good reason to prophylactically administer the drug regimen of Herrstedt, employing netupitant from Bös, palonosetron from Herrstedt, and would have had a reasonable expectation of success that such dosing would effectively treat CINV during the acute and delayed phases of CINV induced by moderately emetogenic chemotherapy.

1237. Accordingly, it is my opinion that claim 35 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

G. Claims 37-38

> **37.** The method of claim 21, wherein said chemotherapy comprises cisplatin.
>
> **38.** The method of claim 21, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

1238. Each of claims 37 and 38 depends from dependent claim 21 and additionally recites that said chemotherapy comprises cisplatin (claim 37) or comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 38).

1239. As I previously addressed above, claim 21 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.A, above.

1240. Herrstedt discloses the chemotherapy comprises cisplatin. Herrstedt explains:

Four phase III trials have investigated the use of aprepitant in patients

receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

1241. Additionally, as I explained above, Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. EX1010 (Herrstedt), Abstract. Herrstedt suggests treating CINV wherein the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin. *Id.*, Table 1 (relevant portions reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy comprises cisplatin (as in claim 37) and where the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (as in claim 38).

1242. Accordingly, it is my opinion that each of claims 37-38 as a whole were also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

H. Claim 39

39. The method of claim 21, wherein said chemotherapy comprises cyclophosphamide.

1243. Claim 39 depends from dependent claim 21 and additionally recites that said chemotherapy comprises cyclophosphamide.

1244. As I previously addressed above, claim 21 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.A, above.

1245. Herrstedt discloses treating CINV where the chemotherapy comprises highly or moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***"). Herrstedt identifies that the NK_1 receptor antagonist is broadly applicable to treating chemotherapy-induced nausea and vomiting.

1246. Herrstedt describes cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (relevant portions reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

1247. Thus, a POSA would have understood Herrstedt to suggest that its antiemetic drug combination is administered to treat CINV induced by highly or moderately emetogenic chemotherapy, where the chemotherapy is cyclophosphamide.

1248. Accordingly, it is my opinion that claim 39 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

I. Claim 43

43. The method of claim 35, wherein:

a) said chemotherapy comprises moderately emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; and

c) said single administration of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant less than 2 hours prior to said chemotherapy.

1249. Claim 43 depends from dependent claim 35 and additionally recites a) said chemotherapy comprises moderately emetogenic chemotherapy; b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; and c) said single administration of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant less than 2 hours prior to said chemotherapy.

1250. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

1251. Herrstedt suggests the chemotherapy is moderately emetogenic chemotherapy. Herrstedt's antiemetic drug combination is administered for treatment of nausea and vomiting induced by chemotherapy including moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by highly or ***moderately emetogenic chemotherapy***").

1252. Although Herrstedt provides detailed summaries for its combination therapy for preventing nausea and vomiting where the emesis inducing event is

highly emetogenic chemotherapy (cisplatin) (EX1010 (Herrstedt), 146), Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. The NK_1 receptor antagonist "increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against acute emesis induced by highly or ***moderately emetogenic chemotherapy***…." EX1010 (Herrstedt), Abstract. Herrstedt describes such moderately emetogenic chemotherapy. *Id.*, Table 1 (relevant portion reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat the CINV induced by moderately emetogenic chemotherapy. Herrstedt describes its antiemetic therapy is applicable for treating CINV induced by said moderately emetogenic chemotherapy. Herrstedt discloses

its NK_1 antiemetic regimen is effective to treat "acute emesis induced by highly or ***moderately emetogenic*** chemotherapy" and that the NK_1 receptor antagonist is "also active in the protection against delayed emesis." EX1010 (Herrstedt), Abstract.

1253. Bös teaches orally administering a therapeutically effective amount of NK_1 receptor antagonists—including netupitant—comprises a range including about 300 mg of netupitant as a free base. For example, Bös teaches:

> In general, in the case of ***oral administration*** a daily ***dosage of about 10 to 1000 mg*** per person of a compound of this invention should be appropriate, although the above upper limit can also be exceeded when necessary.

EX1014 (Bös), 42:5-11. A dose of 300 mg falls squarely within the disclosed range, and very near its midpoint. Further, it is my opinion that a POSA would have recognized a range spanning two orders of magnitude (e.g., 10 to 1,000 mg) to be a common starting point when developing therapeutic dose amounts and it would have been routine to have arrived at an about 300 mg dose through typical optimization. It would have been routine for the POSA to begin dosing studies at the low end of a range and to work their way up to find the lowest dose that achieved desired efficacy. *See, e.g.*, EX1032 (FDA General Considerations for the Clinical Evaluation of Drugs), 5 (desirable to ascertain "the lowest effective dose"), 8 (rising single dose study protocol).

1254. It would have been routine for a POSA in view of the disclosures of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi to perform a dose-ranging study to identify a therapeutically effective dose of netupitant. As described above, Bös provides a clear starting point of 10 to 1,000 mg for such a dose-ranging study. EX1014 (Bös), 42:5-11 ("oral administration a daily dosage of about 10 to 1000 mg per person"). A POSA would have had good reason to implement a routine randomized study with doses ranging from 10 mg to 1,000 mg to determine the most favorable benefit:risk profile (see, e.g., EX1013 (MASCC), 22). A POSA would have had a reasonable expectation of identifying through such a routine dose-ranging study a therapeutically effective amount of netupitant for treating nausea and vomiting.

1255. This routine prior art approach of dose determination is within the scope of exactly what the patent specification contemplates for the claims of the '357 patent. That dose-ranging studies were routinely performed to determine the therapeutically effective amount is also illustrated by the '357 patent specification, which explains:

> As used herein, "therapeutically effective amount" refers to an amount sufficient to elicit the desired biological response. The therapeutically effective amount or dose will depend on the age, sex and weight of the patient, and the current medical condition of the patient. ***The skilled artisan will be able to determine appropriate dosages depending on***

these and other factors in addition to the present disclosure.

EX1002 (’357 patent), 7:55-61. Therefore, the ’357 patent specification confirms that skilled artisans routinely determined therapeutically effective amounts based on common factors. The POSA therefore would have found it routine to arrive at the oral 300 mg therapeutic dose of netupitant. Thus, it is my opinion that the POSA would have had good reason to select a dose of about 300 mg when determining the therapeutically effective amount of netupitant to orally administer to the patient, and would have had a reasonable expectation of success in achieving the desired therapeutic effect with that dose.

1256. The ’357 patent itself does not ascribe any particular or unexpected results associated with the 300 mg dose of netupitant. I have reviewed the ’357 patent and do not observe any particular benefits linked with a 300 mg dose of netupitant specifically. For example, the netupitant-dexamethasone drug interaction study (EX1002 (’357 patent), 15:62-16:32) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*; *see also* ’357 patent, Fig. 4. In a PET receptor occupancy study of netupitant (*id.*, 16:33-57), the highest dose group (again, 450 mg) achieved the greatest duration of blockade of NK_1 receptors because “the decline over time was dose dependent.” *See also id.*, Fig. 5. The 300 mg dose was merely the highest dose evaluated in a clinical efficacy study

(*id.*, Example 5) but even that study simply showed a very small (probably statistically and clinically insignificant) iterative increase of efficacy with increased dose amount. Therefore, based on my review of the '357 patent, there is no particular or unexpected benefit ascribed to the 300 mg dose specifically.

1257. Herrstedt summarizes that, in a study treating CINV induced by moderately emetogenic chemotherapy, the antiemetic combination therapy was tested and showed "a significant benefit." EX1010 (Herrstedt), 146. Herrstedt further discloses that the administration details are provided in the underlying study (EX1034 (Warr)). *Id.* Warr expressly confirms that the addition of an NK_1 receptor antagonist (aprepitant) to a therapeutic regimen of 5-HT_3 receptor antagonist (ondansetron) and dexamethasone provided improved treatment of CINV induced by moderately emetogenic chemotherapy. EX1034 (Warr), Abstract.

1258. Warr confirms that Herrstedt's summarized studies administer the NK_1 receptor antagonist and dexamethasone less than 2 hours prior to chemotherapy. Warr describes its regimen comprises a single administration of dexamethasone comprising about 12 mg of dexamethasone less than 2 hours prior to chemotherapy. Warr explains that "[p]atients were randomly assigned to either an ***aprepitant regimen*** (day 1, APR 125 mg, ondansetron (OND) 8 mg, and ***dexamethasone 12 mg before chemotherapy*** and OND 8 mg 8 hours later; days 2

through 3, APR 80 qd) or a control regimen…." EX1034 (Warr), Abstract; *see also id.*, Table 1 (reproduced below):

Table 1. Study Medication Schedule

Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
Aprepitant (n = 438)			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
Control (n = 428)			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

Thus, Warr details that "the MEC study" of Herrstedt (EX1010 (Herrstedt), 146) treatment regimen comprises a single 12 mg administration. Warr also describes the dexamethasone is administered "30 minutes before chemotherapy" and the NK_1 receptor antagonist is administered "1 hour before chemotherapy" (i.e., each less than 2 hours prior to chemotherapy). *Id.*, Table 1 (above).

1259. Warr describes its dexamethasone is administered in a dosage form independent of the other medications. EX1034 (Warr), Abstract & Table 1 (above). Thus, Warr details that "the MEC study" of Herrstedt (EX1010 (Herrstedt), 146) treatment regimen includes dexamethasone administered in a dosage form independent from the 5-HT_3 and NK_1 receptor antagonists.

1260. A POSA would have been motivated, when developing the fixed dose unit dosage form containing palonosetron and netupitant, to keep dexamethasone in a dosage form independent of said combination unit dosage form. As I explained

above (Section XXIX.A, claim element 21(c)), it was known that when multiple "drugs are used at ***constant dosage***" they may be administered together in a single dosage form. EX1061 (Cromie), 78. Indeed, Cromie indicates that "drugs [] administered at ***constant dosage***" is a prerequisite for a POSA to experience the "considerable practical advantages in giving the required drugs in single formulation." *Id.* In contrast, a POSA would have known that dexamethasone ***is not administered in a constant dosage***. For example, in Herrstedt's triple antiemetic therapy, dexamethasone is administered in a 12 mg dose on the first day for treating moderately emetogenic chemotherapy (EX1034 (Warr), Abstract, Table 1) but is administered in both 12 mg (day one) and 8 mg (days two-four) doses for treating highly emetogenic chemotherapy. EX1039 (Poli-Bigelli), Abstract; EX1037 (Hesketh), 4113. Thus, because dexamethasone is not administered at a constant dosage and varies depending on the emetogenic event, a POSA would have formulated the unit dosage form to include palonosetron and netupitant but would not include dexamethasone. It was obvious to administer the dose of dexamethasone in a dosage form independent of the combination unit dosage form.

1261. Accordingly, it is my opinion that claim 43 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

J. Claim 44

44. The method of claim 35, wherein:

a) said chemotherapy comprises highly emetogenic chemotherapy;

b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy;

c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and

d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

1262. Claim 44 depends from dependent claim 35 and additionally recites a) said chemotherapy comprises highly emetogenic chemotherapy; b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy; c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

1263. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

44(a): a) said chemotherapy comprises highly emetogenic chemotherapy;

1264. I have reproduced above the highly emetogenic (a) element of claim 44. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally

Herrington, and optionally Aloxi teaches or suggests the highly emetogenic element of claim 44(a).

1265. Herrstedt discloses its regimen is used to treat CINV induced by chemotherapy that is highly emetogenic chemotherapy (e.g., cisplatin). Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2–4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2–4 plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

EX1010 (Herrstedt), 146; *id*. (studies involved "patients receiving ***cisplatin-based, highly emetogenic chemotherapy***"). Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1266. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen treats CINV induced by highly emetogenic chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin (highly emetogenic chemotherapy), the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg

on Day 1; oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on Days 2-3; and oral dexamethasone 8 mg on Day 4." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli explains that this NK_1 receptor antagonist regimen "provided superior antiemetic protection compared with standard therapy" without said NK_1 receptor antagonist. *Id.* Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4." EX1037 (Hesketh), 4113. Hesketh describes this NK_1 receptor antagonist regimen "provided consistently superior protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy." *Id.*, Abstract. Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy.

1267. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 44(a).

> **44(b):** b) said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy;

1268. I have reproduced above the 300 mg netupitant (b) element of claim 44. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally

Herrington, and optionally Aloxi teaches or suggests the 300 mg netupitant element of claim 44(b).

1269. Claim limitation 44(b) ("said netupitant is administered orally as the free base in a dose of about 300 mg less than 2 hours prior to said chemotherapy") is identical to claim limitations 43(b). I explained above that claim 43 as a whole, including claim limitation 43(b), was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.I, above. For at least the same reasons, claim limitation 4(b) was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

1270. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 44(b).

> **44(c):** c) said first dose of dexamethasone comprises about 12 mg, in a dosage form independent of said netupitant, administered less than 2 hours prior to said chemotherapy; and;

1271. I have reproduced above the initial dexamethasone (c) element of claim 44. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the initial dexamethasone element of claim 44(c).

1272. Herrstedt discloses its regimen treating CINV induced by highly emetogenic chemotherapy includes prophylactically administered dexamethasone prior to chemotherapy. Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, ***dexamethasone*** and placebo ***day 1*** followed by dexamethasone plus placebo days 2–4 with ondansetron, ***dexamethasone*** and aprepitant ***day 1*** followed by dexamethasone days 2–4 plus aprepitant days 2–3…. The most recently published HEC study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1273. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen includes dexamethasone administered in a dose of about 12 mg less than 2 hours prior to chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin, the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and ***oral dexamethasone 12 mg on Day 1***." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli also explains that "***[t]hirty minutes prior to cisplatin***, all patients received ondansetron and dexamethasone." *Id.*, 3092. Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32

mg and oral ***dexamethasone 12 mg on day 1***." EX1037 (Hesketh), 4113. Hesketh also explains that "***[t]hirty minutes before cisplatin***, all patients received ondansetron (infused over 15 minutes) and ***dexamethasone***." Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy and that those studies administered dexamethasone in a dose of about 12 mg less than 2 hours prior to chemotherapy.

1274. A POSA would have been motivated, when developing the fixed dose unit dosage form containing palonosetron and netupitant, to keep dexamethasone in a dosage form independent of said combination unit dosage form. As I explained above (Section XXIX.A, claim element 21(c)), it was known that when multiple "drugs are used at ***constant dosage***" they may be administered together in a single dosage form. EX1061 (Cromie), 78. Indeed, Cromie indicates that "drugs [] administered at ***constant dosage***" is a prerequisite for a POSA to experience the "considerable practical advantages in giving the required drugs in single formulation." *Id.* In contrast, a POSA would have known that dexamethasone ***is not administered in a constant dosage***. For example, in Herrstedt's triple antiemetic therapy, dexamethasone is administered in a 12 mg dose on the first day for treating moderately emetogenic chemotherapy (EX1034 (Warr), Abstract, Table 1) but is administered in both 12 mg (day one) and 8 mg (days two-four) doses for treating highly emetogenic chemotherapy. EX1039 (Poli-Bigelli),

Abstract; EX1037 (Hesketh), 4113. Thus, because dexamethasone is not administered at a constant dosage and varies depending on the emetogenic event, a POSA would have formulated the unit dosage form to include palonosetron and netupitant but would not include dexamethasone. It was obvious to administer the dose of dexamethasone in a dosage form independent of the combination unit dosage form.

1275. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 44(c).

> **44(d):** d) said second dose comprises about 8 mg of dexamethasone administered on days 2, 3 and 4 following said chemotherapy.

1276. I have reproduced above the subsequent dexamethasone (d) element of claim 44. It is my opinion that the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi teaches or suggests the subsequent dexamethasone element of claim 44(d).

1277. Herrstedt discloses its regimen treating CINV induced by chemotherapy includes dexamethasone administered on days 2, 3 and 4 following chemotherapy. Herrstedt identifies several studies, for example:

> Two of the ***HEC [highly emetogenic chemotherapy]*** studies used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by ***dexamethasone*** plus placebo ***days 2–4*** with ondansetron, dexamethasone and aprepitant day 1 followed by

> ***dexamethasone days 2–4*** plus aprepitant days 2–3…. The most recently published ***HEC*** study used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4.

Herrstedt further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146.

1278. A POSA reviewing Herrstedt would have understood that Herrstedt's antiemetic regimen includes dexamethasone administered as a second dose (i.e., a different dose amount from the day 1 dose) where the dose was about 8 mg administered on days 2, 3 and 4 following chemotherapy. Poli-Bigelli expressly describes that, in treating CINV for patients receiving cisplatin, the "aprepitant group received oral aprepitant 125 mg, intravenous ondansetron 32 mg, and oral dexamethasone 12 mg on Day 1; oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on Days 2-3***; and oral ***dexamethasone 8 mg on Day 4***." EX1039 (Poli-Bigelli), Abstract. Poli-Bigelli explains that this regimen "provided superior antiemetic protection compared with standard therapy" without an NK_1 receptor antagonist. *Id.* Similarly, Hesketh describes its patients "in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral ***dexamethasone 8 mg once daily on days 2 and 3***, and oral ***dexamethasone 8 mg on day 4***." EX1037 (Hesketh), 4113. Hesketh describes this regimen "provided consistently superior

protection against CINV in patients receiving highly emetogenic cisplatin-based chemotherapy." *Id.*, Abstract. Thus Poli-Bigelli and Hesketh confirm that Herrstedt summarizes studies treating CINV induced by highly emetogenic chemotherapy and that those studies administered dexamethasone in a dose of about 8 mg on days 2, 3 and 4 following chemotherapy.

1279. Accordingly, the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi discloses the subject matter recited in claim element 44(d).

1280. Accordingly, it is my opinion that claim 44 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

K. Claim 46

46. The method of claim 35, wherein said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1281. Claim 46 depends from dependent claim 35 and additionally recites said netupitant is effective to treat said CINV during the acute and delayed phases of said CINV.

1282. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

1283. Herrstedt describes treating CINV during the acute and delayed phases of chemotherapy. Herrstedt explains its triple combination antiemetic improves efficacy "against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy" and "is also active in the protection against ***delayed emesis***." EX1010 (Herrstedt), Abstract. A POSA would have known the acute phase refers to the antiemetic protection provided during the first 24 hours following chemotherapy, while the delayed phase is the period 24 to 120 hours after chemotherapy. *Id.*, 143. Herrstedt describes studies treating nausea and vomiting with a triple therapeutic combination and further discloses that the administration details are provided "in the Poli-Bigelli study" and in the Hesketh study. EX1010 (Herrstedt), 146. As I explain above, it would have been obvious to employ netupitant as the NK_1 receptor antagonist in Herrstedt's studies.

1284. Poli-Bigelli expressly confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of CINV. EX1039 (Poli-Bigelli), 3096-3097. For example, Poli-Bigelli describes prevention of nausea via improvement of complete response over periods including the acute and delayed phases, and also explains this parameter is a stand-in for the control of nausea:

> In the assessments of complete response over specific periods after cisplatin, the aprepitant regimen provided a ***substantial improvement*** of 14 percentage points over standard therapy in the prevention of

> ***acute*** symptoms, and a ***highly remarkable improvement*** of about 21 percentage points in the prevention of ***delayed*** CINV.
>
> Because patients were considered treatment failures if they either vomited or took rescue medication to alleviate nausea, ***the complete response endpoint*** not only reflects control of emesis but also indirectly reflects control of nausea.

EX1039 (Poli-Bigelli), 3096. Thus, Poli-Bigelli identified the addition of NK_1 receptor antagonist (aprepitant) as disclosed in Herrstedt's triple therapy combination was effective to treat CINV during the acute phase of CINV, and especially during the delayed phase of chemotherapy induced nausea and vomiting.

1285. Hesketh also confirms administering the combination of Herrstedt treats CINV during the acute and delayed phases of chemotherapy induced nausea and vomiting. EX1037 (Hesketh), 4116-4117. As with Poli-Bigelli, Hesketh explains that Herrstedt's triple therapy combination improved complete response during both acute and delayed phases:

> [T]he addition of a 3-day regimen of aprepitant significantly ***improved complete response*** as compared with standard therapy ***throughout the acute and delayed phases***. The magnitude of the benefit associated with the aprepitant regimen (greater than the minimum difference of 10 percentage points, generally considered to be clinically relevant) was clearly ***both statistically significant and clinically meaningful***, and was particularly marked during the delayed phase.

EX1037 (Hesketh), 4117. Regarding said complete response parameter, "[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (85.4% v 55.8%***; P < .001)." *Id.*, 4115; *see also id.*, Figure 2 (reproduced below).

1286. Hesketh reports that the "percentage of patients with ***complete response*** on days 1 to 5 was significantly higher in the aprepitant group (72.7% [n = 260] v 52.3% in the standard therapy group [n = 260]), ***as were the percentages on day 1, and especially on days 2 to 5***." EX1037 (Hesketh), Abstract. As described above, the acute phase is hours 0-24 (i.e., day 1) and the delayed phase is hours 24-120 (i.e., days 2 to 5). Hesketh explains improvement was seen with the triple antiemetic therapy:

> For the primary efficacy comparison, Figure 2 shows the proportions of patients in each treatment group who had ***complete response*** overall and in the acute and delayed phases. The aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both ***the acute phase (89.2% v 78.1%***; P < .001), and ***even more notably, the delayed phase (75.4% v 55.8%***; P < .001).

EX1037 (Hesketh), 4115; *see also id.*, Figure 2 (reproduced below).

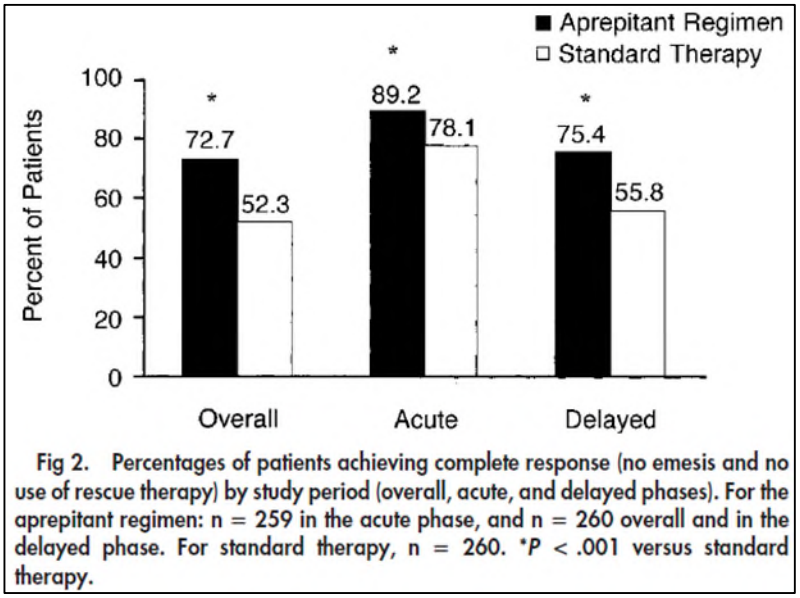


Fig 2. Percentages of patients achieving complete response (no emesis and no use of rescue therapy) by study period (overall, acute, and delayed phases). For the aprepitant regimen: n = 259 in the acute phase, and n = 260 overall and in the delayed phase. For standard therapy, n = 260. *$P < .001$ versus standard therapy.

A POSA would therefore have understood, based on Hesketh's complete response results, that administration of Herrstedt's triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV. Indeed, Hesketh explains that Herrstedt's triple therapy combination ("aprepitant group") was overall superior to the standard therapy (without aprepitant):

> Regardless of the specific end point, ***response rates overall and in the acute and delayed phases were consistently greater*** for the aprepitant group than for standard therapy. In particular, for the end points of no emesis, complete response, and ***complete protection*** (which incorporates both emesis and nausea assessment), the differences were statistically significant, which provides convincing evidence of efficacy of the aprepitant regimen in the prevention of CINV. Although the groups did not differ statistically for total control, no nausea, and no significant nausea, rates for these end points were ***consistently numerically higher in the aprepitant group***. The higher

> response rates of these end points in the aprepitant group, interpreted in the context of a significantly less frequent need for rescue therapy, indicate that aprepitant provided some benefit against nausea as well as emesis.

EX1037 (Hesketh), 4117. Thus, the Poli-Bigelli and Hesketh studies further confirm Herrstedt's report that administration of the triple therapy combination is effective to treat CINV during the acute and delayed phases of CINV.

1287. Accordingly, it is my opinion that claim 46 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

L. Claims 47-48

> **47.** The method of claim 35, wherein said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy.
>
> **48.** The method of claim 35, wherein said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

1288. Claim 47 depends from dependent claim 35 and additionally recites said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy. Claim 48 depends from dependent claim 35 and additionally recites said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

1289. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

1290. A POSA reviewing Herrstedt would have understood that the antiemetic therapy of Herrstedt was effective to prevent and reduce the severity of nausea in patients during the acute and delayed phases of CINV. For example, Herrstedt describes its antiemetic dosing combination provided an improvement in the "complete response," as its primary endpoint which Herrstedt defines as "no emesis and no rescue therapy on days 1-5 postcisplatin." EX1010 (Herrstedt), 146. Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of nausea and vomiting in response to highly emetogenic chemotherapy (i.e., cisplatin) during the acute phase and the delayed phase. EX1039 (Poli-Bigelli), 3096-3097; *see also id.*, Table 2 (below).

TABLE 2
Percentages of Patients who Reached Secondary and Exploratory Efficacy Endpoints, by Study Phase and Treatment Group

	Overall (Days 1–5)		Acute (Day 1)		Delayed (Days 2–5)	
Treatment group	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 261 patients)[a]	Standard therapy (n = 263 patients)[a]	Aprepitant regimen (n = 260 patients)[a]	Standard therapy (n = 263 patients)[a]
No emesis	66[b]	44	84[b]	69	72[b]	48
No rescue	82[b]	73	96[b]	90	83[c]	74
Complete protection	56[b]	41	80[b]	65	61[b]	44
Total control	44[b]	32	64	57	50[b]	34
No nausea	49[c]	39	n/p	n/p	53[b]	40
No significant nausea	71	64	n/p	n/p	73	65

n/p: Analysis not performed; complete protection: no emesis, no rescue therapy, and nausea visual analog scale (VAS) score <25 mm; total control: no emesis, no rescue therapy, and nausea VAS score <5 mm.
[a] Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual endpoints.
[b] $P < 0.01$ compared with standard therapy.
[c] $P < 0.05$ compared with standard therapy.

Although Poli-Bigelli indicates evaluation of nausea alone was "not performed" during the acute phase, the "***complete protection***" parameter requires no significant nausea. *Id.*, 3092; *id.* ("acute-phase analysis was not planned" "for the no nausea and no significant nausea endpoints"). Additionally, Poli-Bigelli teaches that "the complete response endpoint not only reflects control of emesis but also ***indirectly reflects control of nausea***" and reports that the triple-therapy combination improved complete response by 14 percentage points during the acute period, and "***a highly remarkable improvement*** of about 21 percentage points in the prevention of delayed CINV." *Id.*, 3096. Thus, Poli-Bigelli suggests the therapeutic regimen is effective to prevent and reduce the severity of nausea following the administration of chemotherapy.

1291. Hesketh also confirms the antiemetic dosing combination of Herrstedt is effective to prevent and reduce the severity of nausea during both the acute phase and the delayed phase. EX1037 (Hesketh), 4115-4116 & Table 2 (below).

Table 2. Percentages of Patients Reaching Secondary or Exploratory Efficacy End Points by Study Phase and Treatment Group (nominal *P* values reported)

	Acute (day 1)		Delayed (days 2-5)		Overall (days 1-5)	
Treatment Group	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡	Aprepitant Regimen (n = 260)‡	Standard Therapy (n = 260)‡
No emesis	90.0†	79.3	80.8†	58.8	77.7†	55.0
No rescue	94.2*	88.8	81.2*	73.5	80.8†	70.8
Complete protection	84.8†	74.6	66.4†	51.5	63.4†	49.2
Total control	70.7	64.2	49.0	42.7	45.5	40.0
No nausea	72.3§	69.1§	51.0	47.7	47.5	44.2
No significant nausea	90.6§	86.5§	75.3	68.5	73.2	66.0

NOTE. Complete protection indicates no emesis, no rescue therapy, and nausea visual analog scale score < 25 mm; total control indicates no emesis, no rescue therapy, and nausea visual analog scale score < 5 mm.

*$P < .05$ versus standard therapy (significance based on logistic regression model).

†$P < .01$ versus standard therapy (significance based on logistic regression model).

‡Because not every patient provided complete efficacy data, very slight variability (1 to 4 patients) occurred in the total numbers of patients across analyses for individual end points.

§Analysis not planned.

1292. Therefore, a POSA would have had good reason to prophylactically administer the drug combination of Herrstedt, employing netupitant from Bös, the palonosetron of Herrstedt, and would have had a reasonable expectation of success that such dosing would treat CINV and the regimen would be effective to prevent and reduce the severity of nausea in a patient following administration of chemotherapy.

1293. Accordingly, it is my opinion that each of claims 47 and 48 as a whole were also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

M. Claims 49-50

49. The method of claim 35, wherein said chemotherapy comprises cisplatin.

50. The method of claim 35, wherein said chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin.

1294. Each of claims 49 and 50 depends from dependent claim 35 and additionally recites that said chemotherapy comprises cisplatin (claim 49) or comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (claim 50).

1295. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

1296. Herrstedt discloses the chemotherapy comprises cisplatin. Herrstedt explains:

> Four phase III trials have investigated the use of aprepitant in patients receiving ***cisplatin-based, highly emetogenic chemotherapy*** or a combination of cyclophosphamide plus an anthracycline. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 ***postcisplatin***', was the primary end-point in all studies.

EX1010 (Herrstedt), 146. Thus, the studies described in Herrstedt evaluating the antiemetic combination are used to treat nausea and vomiting induced by the highly emetogenic chemotherapy, cisplatin. EX1010 (Herrstedt), 146.

1297. Additionally, as I explained above, Herrstedt is not limited to treating nausea and vomiting in response to cisplatin. Herrstedt identifies that the NK_1 receptor antagonist is more broadly applicable to treating chemotherapy-induced nausea and vomiting. EX1010 (Herrstedt), Abstract. Herrstedt suggests treating CINV wherein the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin. *Id.*, Table 1 (relevant portions reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

Thus, a POSA would have understood Herrstedt to disclose its antiemetic drug combination is administered to treat CINV where the chemotherapy comprises cisplatin (as in claim 49) and where the chemotherapy comprises carboplatin, cisplatin, oxaliplatin, or doxorubicin (as in claim 50).

1298. Accordingly, it is my opinion that each of claims 49-50 as a whole were also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

N. Claim 51

39. The method of claim 35, wherein said chemotherapy comprises cyclophosphamide.

1299. Claim 51 depends from dependent claim 35 and additionally recites that said chemotherapy comprises cyclophosphamide.

1300. As I previously addressed above, claim 35 was obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Section XXIX.F, above.

1301. Herrstedt discloses treating CINV where the chemotherapy comprises highly or moderately emetogenic chemotherapy. EX1010 (Herrstedt), Abstract (efficacy of the drug combination on "emesis induced by ***highly or moderately emetogenic chemotherapy***"). Herrstedt identifies that the NK_1 receptor antagonist is broadly applicable to treating chemotherapy-induced nausea and vomiting.

1302. Herrstedt describes cyclophosphamide is an emetogenic chemotherapy, classified as highly emetogenic or moderately emetogenic depending on its dose. *Id.*, Table 1 (relevant portions reproduced below).

Table 1.

Emetic potential of cytotoxins.

Risk of emesis 0–24 hr after initiation of chemotherapy, if no antiemetics are given	
High (>90%)	Intravenous
	Cisplatin
	Mechloretamine, streptozocin, dacarbazine
	Cyclophosphamide >1500 mg/m^2
	Oral
	Procarbazine
Moderate (30–90%)	Intravenous
	Oxaliplatin
	Cytarabine >1000 mg/m^2
	Carboplatin
	Ifosfamide
	Cyclophosphamide <1500 mg/m^2
	Doxorubicin, epirubicin, daunorubicin, idarubicin
	Irinotecan
	Oral
	Cyclophosphamide, etoposide, temozolomide
	Vinorelbine, imatinib

1303. Thus, a POSA would have understood Herrstedt to suggest that its antiemetic drug combination is administered to treat CINV induced by highly or moderately emetogenic chemotherapy, where the chemotherapy is cyclophosphamide.

1304. Accordingly, it is my opinion that claim 51 as a whole was also obvious over Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi.

O. Motivation to Combine

1305. I explained above why a person having ordinary skill in the art would have been motivated to combine the prior art references of Herrstedt, Bös, Bonadeo, and optionally Herrington. Section XXVIII.B.

1306. A POSA also had good reason to develop and administer a single unit dosage form for administering therapeutically effective amounts of palonosetron and netupitant. A POSA considering dose formulations of palonosetron and concomitantly administered therapeutics (e.g., NK_1 receptor antagonists such as netupitant) would have had good reason to apply the teachings of Bonadeo. Bonadeo discloses soft capsules containing palonosetron, and suggests the capsules can be formulated to contain additional pharmaceutical actives. EX1017 (Bonadeo), 16; *see also id.*, 5 ("reference to 'an active pharmaceutical agent' includes more than one active pharmaceutical agent."). As I describe above (Section XXIX.A), there was good reason to administer palonosetron with netupitant at the same time. For example, Cromie describes that where multiple drugs are administered to patients concomitantly and they are administered in constant dosages, "there are considerable practical advantages in giving the required drugs in a single formulation. Such combination formulations give greater convenience and safety for patient and doctor and reduce the risk of errors in medication." EX1058 (Cromie), 78.

1307. The persons having ordinary skill in the art also would have been motivated to administer palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base. As I explained above, this exact amount had been disclosed in the prior art (e.g., Aloxi, Bonadeo) as being therapeutically effective and the POSA would have been motivated to use the proven therapeutically effective dose amounts. XXIX.A, above. Furthermore, Aloxi describes an FDA-approved oral capsule of palonosetron HCl that was shown to provide antiemetic effect when administered to patients receiving emetogenic chemotherapy, showing the therapeutically effective amount is 0.50 mg of palonosetron hydrochloride based on the weight of the free base. EX1015 (Aloxi), 2-4. Thus, the POSA would have had good reason to use the Bonadeo and Aloxi capsule of palonosetron HCl in developing its administration of palonosetron and netupitant.

P. Reasonable Expectation of Success

1308. I explained above why a person having ordinary skill in the art would have had a reasonable expectation of success in combining the teachings from the prior art references of Herrstedt, Bös, Bonadeo, and optionally Herrington. Section XXVIII.C.

1309. The POSA also would have had a reasonable expectation of success in formulating a single dosage form containing palonosetron and netupitant because

Bonadeo suggests its formulations are modifiable to contain multiple active ingredients. EX1017 (Bonadeo), 16 ("Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives from the liquid core into the body."); *id.*, 5 ("reference to 'an active pharmaceutical agent' includes more than one active pharmaceutical agent").

1310. Additionally, it was well-known in the art that fixed dose administrations (i.e., administrations containing at least two active pharmaceutical ingredients) were routinely formulated. For example, Sanso explains numerous prior art references disclosed capsules for oral delivery of multiple active pharmaceutical ingredients. EX1060 (Sanso), 1:58-2:8. Sanso explicitly teaches a "pharmaceutical dosage form particularly suitable for the administration of active principles in multiple therapies" using "a double capsule where in an internal capsule is placed inside an external one" and each "internal and external capsule includes one or more active principles." *Id.*, Abstract. Verifying the routine nature of such combination administration, Sanso explains its dose form can be created using "capsules already on the market." *Id.*, 3:57-4:43.

1311. The POSA also would have had a reasonable expectation of success in using the palonosetron HCl capsules of Bonadeo and Aloxi to in the formulation for administering the fixed dose combination of palonosetron and netupitant. Aloxi

explains the orally administered palonosetron HCl capsules were as efficacious as the previously-FDA-approved intravenous formulation. EX1015 (Aloxi), 4 (non-inferiority studies). Additionally, Aloxi provides clinical studies showing the 0.56 mg palonosetron HCl capsules (corresponding to 0.50 mg palonosetron weight by free base) were therapeutically effective in treating CINV, leading to FDA approval for prophylaxis with emetogenic chemotherapy. *Id.*, 2, 4. Therefore, the POSA would have had a reasonable expectation of success that Aloxi's (and Bonadeo's) palonosetron HCl capsules would treat CINV when incorporated into a single unit formulation with netupitant.

1312. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXX. ['357 PATENT GROUND 8] '357 PATENT CLAIMS 36 AND 45 WERE OBVIOUS OVER HERRSTEDT, BÖS, BONADEO, HARGREAVES, OPTIONALLY HERRINGTON, AND OPTIONALLY ALOXI

1313. For the reasons discussed in detail below, it is my opinion that each of claims 36 and 45 of the '357 patent was obvious as a whole. The obviousness of claims 36 and 45 is exemplified by disclosures in the Herrstedt, Bös, Bonadeo, Hargreaves, optionally Herrington, and optionally Aloxi references.

1314. I have evaluated below whether the combination of Herrstedt, Bös, Bonadeo, Hargreaves, optionally Herrington, and optionally Aloxi discloses each and every element of each of claims 36 and 45 of the ’357 patent. I have also analyzed whether a person having ordinary skill in the art before the critical date would have had good reason to combine these references in a manner that satisfies each claim as a whole with a reasonable expectation of success. As I explain in detail below, the answer to each of these questions is an unequivocal “yes.”

A. Claims 36, 45

> **36.** The method of claim 21, wherein said netupitant occupies at least 70% of said patient’s striatum NK1 receptors ninety-six hours after said administration.
>
> **45.** The method of claim 35, wherein said netupitant occupies at least 70% of said patient’s striatum NK1 receptors ninety-six hours after said administration.

1315. Claims 36 and 45 depend from dependent claims 21 and 35, respectively, and additionally recites said netupitant occupies at least 70% of said patient’s striatum NK1 receptors ninety-six hours after said administration.

1316. As I previously addressed above, each of claims 21 and 35 were obvious over the combination of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. *See* Sections XXIX.A, XXIX.F, above.

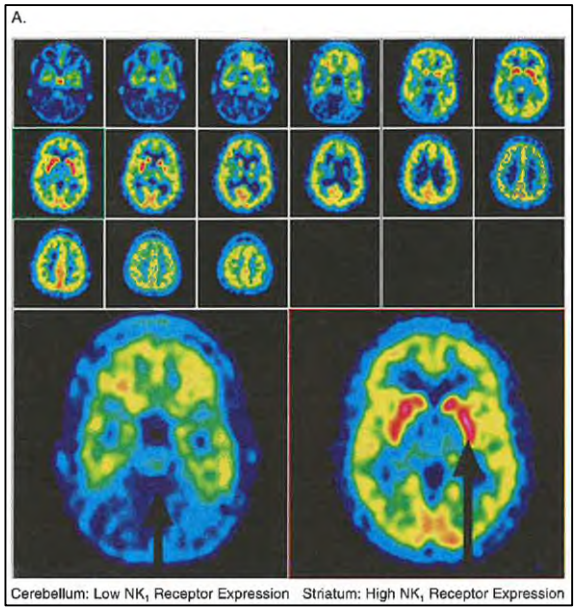
1317. It would have been obvious that the netupitant occupies at least 70% of a patient’s striatum NK_1 receptors ninety-six hours after administration of the netupitant.

1318. The NK_1 receptor antagonist netupitant enters systemic circulation and crosses the blood brain barrier to occupy NK_1 receptors in the striatum. Bös describes netupitant as belonging to a family of compounds that are administered orally. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"). Orally administered netupitant does not act locally at the place of administration. Instead, a POSA in the field would have known that NK_1 receptor antagonists, to be therapeutically effective, interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as striatum…."), Fig. 4. A POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system.

1319. Hargreaves explains that for NK_1 receptor antagonists to be therapeutically effective, they must interfere with Substance P in the central nervous system—with the striatum of the brain having a particularly abundant density of NK_1 receptors. EX1012 (Hargreaves), 21-23 ("The highest [^{18}F]SPA-RQ activity was found in brain regions with high NK_1 receptor density, such as

striatum…."), Fig. 4. Bös describes netupitant has high affinity for the NK_1 receptor antagonist (EX1014 (Bös), 18:42-48) and belongs to a family of compounds that are therapeutically effective when administered. EX1014 (Bös), 42:5-11 ("in the case of oral administration a daily dosage of about 10 to 1000 mg per person of a compound of this invention should be appropriate"); *id.*, 18:64-19:30 (in vivo testing confirming efficacy). Hargreaves' data demonstrate that aprepitant passes into the CNS and binds to NK_1 receptors, including in the striatum.

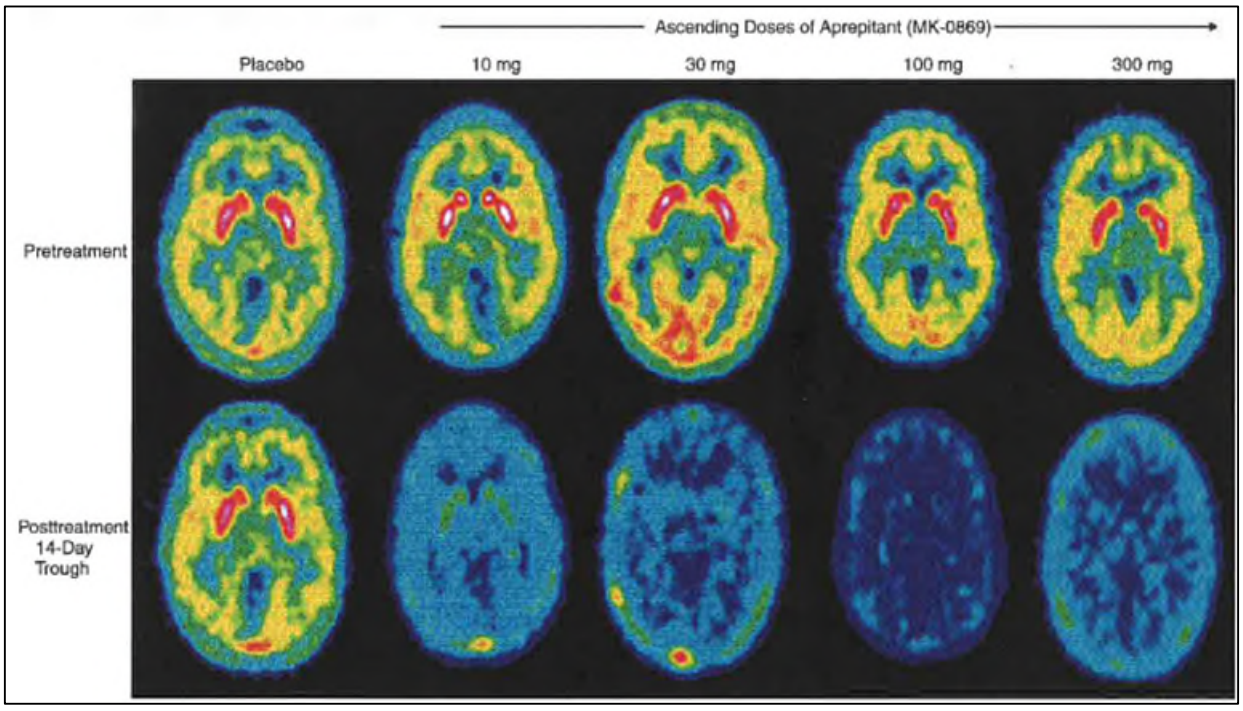
1320. Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum. The striatum is the densest location of NK_1 receptors, as shown by Hargreaves' Positron Emission Tomography (PET) images. EX1012 (Hargreaves), Fig. 4(A) (reproduced below):



Hargreaves also shows therapeutic success through the targeted inhibition of NK_1 receptors in the striatum. Hargreaves explains that, comparing the NK_1 receptor antagonist aprepitant to placebo:

> After treatment, a dose-proportional reduction in tracer binding to NK_1 receptors in the striatum was observed with aprepitant, but not with placebo (Figure 5). It is noteworthy that [^{18}F]SPA-RQ binding in other regions of the brain known to express NK_1 receptors (e.g., amygdala) was also reduced, in line with observations made in the striatum. On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A).

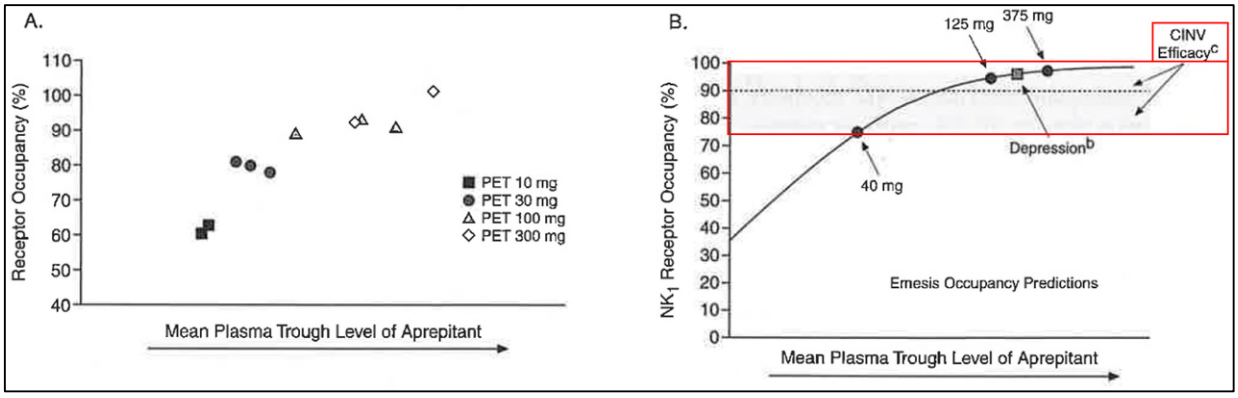
EX1012 (Hargreaves), 21-23; *see also id.*, Fig. 5 (reproduced below).



1321. Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting:

> On the basis of these findings, a plasma concentration vs. receptor occupancy relationship was established (Figure 6A). The data suggest that a trough concentration following treatment with the 10-mg dose of aprepitant corresponds to approximately 60% receptor occupancy, whereas the occupancy of ≥ 90% of NK_1 receptors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration—receptor occupancy curves showed that ***high levels of NK_1 receptor occupancy were associated with*** significant antidepressant effects and ***optimal activity against CINV***. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS (Figure 6B), whereas ***the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B)***.

EX1012 (Hargreaves), 23. Reproduced below is an annotated version of Hargreaves Fig. 6.



Hargreaves Fig. 6B shows "CINV Efficacy" for antiemetic therapy beginning at approximately 75% of NK_1 receptor occupancy, corresponding with a 40 mg dose of aprepitant. *Id.* Accordingly, the combination of Herrstedt, Bös, Hargreaves, and optionally Herrington teaches or suggests netupitant occupies at least 70% of said patient's striatum NK1 receptors after administration as recited in claim 18. Based on Hargreaves' prior art modeling, a POSA would have found it obvious that prophylactically (prior to chemotherapy) administering a therapeutically-effective amount of NK_1 receptor antagonist (e.g., netupitant) occupying 75% (at least 70%) of NK_1 receptors in the striatum ninety-six hours after administration would be very likely to be efficacious for treating CINV.

1322. Additionally, the "at least 70%" occupancy limitation encompasses the "at least 75%" occupancy threshold that the prior art taught naturally accompanied administration of a therapeutically effective amount of an NK_1 receptor antagonist for the treatment of emesis. I can discern no reasonable distinction between this claim limitation and what was disclosed in the prior art. Indeed, my review of the prosecution of the application that issued as the '297 patent indicates that it was the unrebutted understanding of the examiner that this occupancy was an inherent property of administering a therapeutically-effective amount of netupitant that satisfies the "at least 70%" occupancy limitation. For example, the examiner stated that netupitant occupying at least 70% of a patient's

striatum NK_1 receptors seventy-two hours after administration is an inherent feature of administering a therapeutically effective dose of netupitant. EX1008, 120; Section V.D, above. Furthermore, seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant (3 days (and 4 days) into the 5-day course of treatment). *See, e.g.*, EX1014 (Bös), 19:7-38. The applicant did not disagree with the examiner's position. EX1008, 155; Section V.D, above. The '357 patent specification reports this is a characteristic of netupitant itself: "netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and [] less than 20 or 30% of netupitant is released from striatum NK_1 receptors ***even ninety-six hours*** after administration." EX1002 ('357 patent), 4:37-51. The patentee's admissions and lack of dispute on inherency with the examiner are consistent with my understanding.

1323. Accordingly, it is my opinion that each of claims 36 and 45 as a whole were obvious over Herrstedt, Bös, Bonadeo, Hargreaves, optionally Herrington, and optionally Aloxi.

B. Motivation to Combine

1324. I explained above why a person having ordinary skill in the art would have been motivated to combine the prior art references of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. Section XXIX.O.

1325. To evaluate the dose necessary to achieve the minimal effective therapeutic dose, the POSA would have had good reason to evaluate the NK_1 receptor occupancy disclosed by Hargreaves. Hargreaves taught practitioners to administer doses of NK_1 receptor antagonist in an amount that will result in at least about 75% of NK1 receptors occupied in the striatum (EX1012 (Hargreaves), 23 & Fig. 6(B)). Hargreaves explains that doses of aprepitant of greater than or equal to 100 mg resulted in NK_1 receptor occupancy in excess of about 90%. *Id.* Thus, the POSA would have had good reason to similarly use NK_1 receptor occupancy to determine therapeutically effective dose amounts of other NK_1 receptor antagonists, such as netupitant, when developing the single unit dosage form.

C. Reasonable Expectation of Success

1326. I explained above why a person having ordinary skill in the art would have had a reasonable expectation of success in combining the teachings from the prior art references of Herrstedt, Bös, Bonadeo, optionally Herrington, and optionally Aloxi. Section XXIX.P.

1327. The POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves, as I explained previously. Section XXX.A, above. The POSA would have understood that such studies were routinely conducted, and because the receptor occupancy being evaluated would be the same

(NK_1 receptors in the striatum), it would have been routine to evaluate the effect of netupitant in the same manner described in Hargreaves.

1328. Accordingly, the POSA had good reason to combine Herrstedt, Bös, Bonadeo, Hargreaves, optionally Herrington, and optionally Aloxi to arrive at the claimed invention, and the POSA would have had a reasonable expectation of success in making the modifications to arrive at the claimed invention.

XXXI. NO UNEXPECTED RESULTS

1329. In light of the prior art, it is my opinion that nothing that was presented in the challenged patents or during the prosecution of the challenged patents shows unexpected results. For ease of reference, I provide a summary of why there are no unexpected results with reference to the '826 patent below unless noted otherwise. My evaluation and conclusions apply equally to each of the patents involved in this patent family.

A. Aprepitant shows efficacy for nausea

1330. While prosecuting the application that issued as the '826 patent, the patent applicant (Helsinn) sought to distinguish the new NK_1 receptor antagonist—netupitant—from known NK_1 receptor antagonist—aprepitant. In particular, Helsinn contended that "aprepitant's effect was limited principally to vomiting, not nausea, and that aprepitant did not provide as much benefit during the acute phase [i.e., 0-24 hours] of CINV." EX1001 ('826 patent), 2:12-26. The '826 patent

argues “it has unexpectedly been discovered that netupitant is active against nausea” (EX1001 (’826 patent), 4:37-39), but as I explain below, aprepitant was also active against nausea—thus there is nothing surprising about the effect. The applicant also argued during prosecution that prior art “did not distinguish between vomiting and nausea as separate therapeutic targets, and instead lumped them together as one indication commonly referred to as CINV.” EX1005 (file history of ’462 application), 328-329. The applicant sought to distinguish the method using netupitant (in substitution for aprepitant) because “the claimed regimen treats both nausea and vomiting.”

1331. Similarly, during prosecution of the application that issued as the ’297 patent, the patent applicant argued there were unexpected results with the combination of netupitant and palonosetron as compared to aprepitant because, in its selected trials of aprepitant, “in none of these trials was aprepitant able to demonstrate a statistically significant effect against nausea or significant nausea. This was true throughout the acute and delayed phases of emesis, and it was true regardless of whether moderately emetogenic chemotherapy (MEC) or highly emetogenic chemotherapy (HEC) was administered.” EX1008 (file history of ’050 application), 181. The applicant asserted that a POSA “would not have had a reasonable expectation of successfully treating nausea from the combination of

netupitant and palonosetron" because aprepitant allegedly did not provide such effect. *Id.*, 181-182.

1332. As I detail below, contrary to Helsinn's representations to the USPTO, experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea.

1. Emend label

1333. The '826 patent specification proclaims that the Emend label shows that "[w]hen tested against nausea in humans, aprepitant was unable to induce a significant reduction in the incidence or severity of nausea following moderately or highly emetogenic chemotherapy when compared to 5-HT3 antagonist alone." EX1001 ('826 patent), 2:16-21. During prosecution, the applicant reproduced portions of the Emend label to argue that aprepitant "did not achieve statistically significant reduction in either nausea or significant nausea[.]" EX1005 (file history of '462 application), 330.

1334. But the Emend label, in my opinion, shows reduction of nausea (and in particular reducing significant nausea) for patients. Further, while statistical significance was not calculated for nausea parameters, the "***complete protection***" value ***includes*** a lack of significant nausea in its metric. EX1030 (Emend label), 7 ("***complete protection*** (defined as no emetic episodes, no use of rescue therapy, ***and a maximum nausea visual analogue scale [VAS] score <25 mm*** on a 0 to 100

mm scale)"). In other words, when evaluating whether a patient achieved "***complete protection***," the Emend label requires (1) ***no*** emetic episodes; (2) ***no*** rescue therapy; **and** (3) ***no significant nausea***. Table 1 of the Emend label shows results of the first of two studies described in the label. It indicates substantial improvement of ***complete protection*** for overall, acute phase, and delayed phase parameters, and identifies the delayed phase and overall parameters were also statistically significant.

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	73	52	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	89	78	<0.001
Delayed phase‖	75	56	<0.001
Complete Protection			
Overall	63	49	0.001
Acute phase	85	75	NS*
Delayed phase	66	52	<0.001
No Emesis			
Overall	78	55	<0.001
Acute phase	90	79	0.001
Delayed phase	81	59	<0.001
No Nausea			
Overall	48	44	NS**
Delayed phase	51	48	NS**
No Significant Nausea			
Overall	73	66	NS**
Delayed phase	75	69	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.
‖Delayed phase: 25 to 120 hours post-cisplatin treatment.
*Not statistically significant when adjusted for multiple comparisons.
**Not statistically significant.
Visual analogue scale (VAS) score range: 0 mm = no nausea; 100 mm = nausea as bad as it could be.

EX1030 (Emend label), Table 1.

1335. Additionally, although not calculated for statistical significance, a POSA would have recognized an improvement for treatment of nausea (and in particular for treatment of significant nausea) represented in the Emend Label Table 1 data. *Id.* (e.g., 66% → 73% overall in significant nausea). A POSA would have therefore understood that aprepitant likely had an effect on nausea—most notably with significant nausea (having VAS > 25 mm). This was true during the delayed phase as well as overall (which includes acute and delayed phases).

1336. The Emend label shows similar benefits with the results of a second study. The second study shows "***complete protection***" with statistical significance for ***each of*** the overall, acute phase, and delayed phase timelines.

ENDPOINTS	Aprepitant Regimen (N = 261)† %	Standard Therapy (N = 263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

†N: Number of patients (older than 18 years of age) who received cisplatin, study drug, and had at least one post-treatment efficacy evaluation.
‡Overall: 0 to 120 hours post-cisplatin treatment.
§Acute phase: 0 to 24 hours post-cisplatin treatment.

Id., Table 2. As I explained above, the "***complete protection***" endpoint includes the requirement of ***no significant nausea***. Thus, a POSA would have understood this data to illustrate an improvement in the patients receiving aprepitant, ***including*** a decrease of significant nausea. Furthermore, a POSA would have recognized an even greater improvement for treatment of nausea in this study cohort (and in particular for treatment of significant nausea), even if not calculated for statistical significance. *Id.* (e.g., 64% → 71% overall in significant nausea; 39% → 49% overall in nausea). The POSA therefore reasonably would have expected aprepitant had a beneficial effect on nausea, notwithstanding the lack of calculated statistical significance for those specific parameters.

1337. The Emend label also describes that patient-reported outcomes evidenced that aprepitant decreased nausea. It reports:

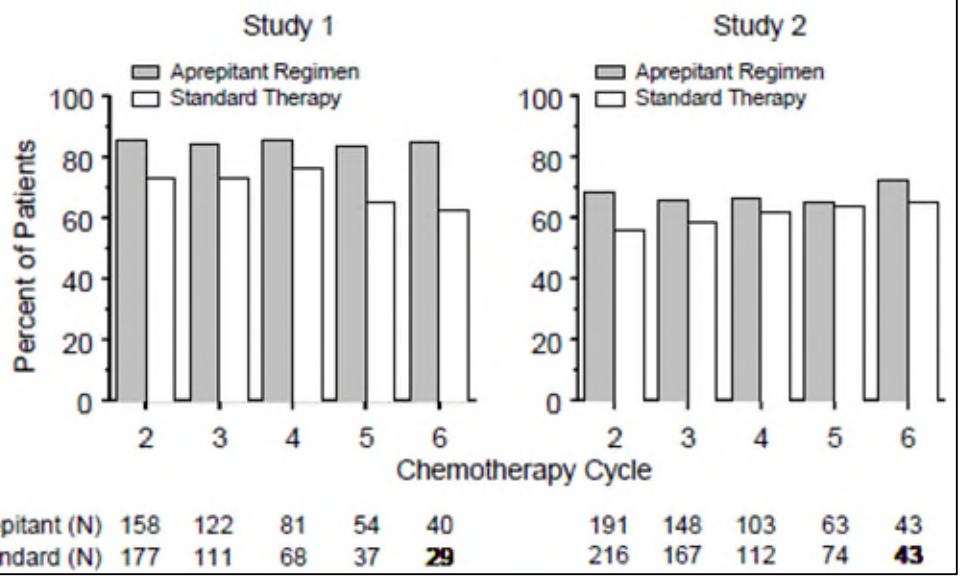
> In each of the 2 studies, a higher proportion of patients receiving the aprepitant regimen reported minimal or no impact of nausea and vomiting on daily life (Study 1: 74% versus 64%; Study 2: 75% versus 64%)."

EX1030 (Emend label), 6. In other words, patients themselves reported a significant improvement on their daily lives due to a more limited impact of nausea and vomiting, as opposed to a treatment group without aprepitant.

1338. Additionally, the Emend label includes a summary of patients that had no emesis ***and*** no significant nausea following highly emetogenic chemotherapy.

Id., 6 ("In the same 2 clinical studies, patients continued into the Multiple-Cycle extension for up to 5 additional cycles of chemotherapy. The proportion of patients with ***no emesis and no significant nausea*** by treatment group at each cycle is depicted in Figure 3."). Figure 3 of the Emend label illustrates an improvement across each cohort for no emesis ***and*** no significant nausea when using the aprepitant combination.

Figure 3: Proportion of Patients Receiving Highly Emetogenic Chemotherapy With No Emesis and No Significant Nausea by Treatment Group and Cycle



	Study 1					Study 2				
Aprepitant (N)	158	122	81	54	40	191	148	103	63	43
Standard (N)	177	111	68	37	**29**	216	167	112	74	**43**

Id., Fig. 3.

1339. It is therefore my opinion that a POSA would have understood the Emend label to support what the FDA approved it for—antiemetic therapy for chemotherapy-induced nausea ***and*** vomiting. *See, e.g.*, EX1030 (Emend label), 8:

INDICATIONS AND USAGE

EMEND for Injection, in combination with other antiemetic agents, is indicated for the:

- prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of highly emetogenic cancer chemotherapy including high-dose cisplatin
- prevention of nausea and vomiting associated with initial and repeat courses of moderately emetogenic cancer chemotherapy (see DOSAGE AND ADMINISTRATION).

Contrary to the applicant's (and the declarants') argument made during prosecution, a POSA would not have understood this label to merely show an effect on vomiting without any effect on nausea. I therefore disagree with the applicant's conclusion that its purported invention differs from prior art because the combination of netupitant, palonosetron, and dexamethasone treats both nausea and vomiting.

1340. Accordingly, it is my opinion that a POSA would have understood Emend label to show that aprepitant had a beneficial effect on treating both nausea and vomiting.

2. Example 5 of the '826 Patent

1341. Contrary of the patent applicant's contentions, Example 5 of the '826 patent (EX1001 ('826 patent), 16:62-19:43) illustrates that aprepitant has an effect on nausea comparable to netupitant. Data presented in Table 6 of the '826 patent corresponds to columns 1, 2, and 6 of Table 2 from the 132 Declaration:

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

EX1001 (’826 patent), Table 6.

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)

[nr] Data Not Reported

[ncs] Non-Comparative Study; statistical significance not evaluated

EX1005 (file history of ’462 application), 346. The Declaration Table 2 selectively excised information from the larger data set provided in ’826 Table 6. *See* above (acute and delayed values missing from Declaration Table 2).

1342. Example 5 of the ’826 patent specification was never designed to compare netupitant against aprepitant—and the specification’s Example 5 never alleges any benefits of netupitant versus aprepitant. Example 5 of the ’826 patent explains:

> The ***objective of the study was to compare*** the efficacy and safety of three single oral doses of ***netupitant combined with oral palonosetron*** and given with dexamethasone, ***versus oral palonosetron-alone given with dexamethasone*** (without netupitant) for the prevention of highly emetogenic chemotherapy (HEC)-induced nausea and vomiting. The FDA-approved oral aprepitant regimen given with IV ondansetron and dexamethasone was included in the study as an active comparator for exploratory purposes. The FDA-approved oral palonosetron 0.5 mg dose was used in each applicable treatment group in this study.

EX1001 (’826 patent), 17:4-14. Example 5 of the ’826 patent never asserts that the combination of palonosetron and netupitant was better than ondansetron and aprepitant for treatment of nausea. Instead, it proclaims the combination including netupitant is better than the treatment without an NK_1 receptor antagonist (“Palo alone”). *Id.*, Example 5.

1343. The data presented in the affidavit and considered by the examiner compared ***the highest dose of netupitant*** with palonosetron (EX1001 ('826 patent), Table 6, "Palo + Netu 300 mg" column) with an aprepitant and ondansetron combination (*id.*, "Aprepitant Regimen" column). Even if a POSA were to assume these two data sets were comparable, this data shows—at best—only marginal improvement between the ***highest dose*** of netupitant compared to a standard aprepitant combination for the treatment of nausea.

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis

**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

EX1001 (’826 patent), Table 6. The reported percentage of patients overall having no significant nausea differed between the two groups by less than 4%, while the percentage of patients overall having no nausea differed by only 3.3%. *Id.* A POSA would have understood these results to show ***comparable effect*** on nausea, and thus there is no unexpected result with the combination of netupitant and palonosetron as compared to aprepitant and ondansetron. I note that this difference in efficacy is less than that reported in the Emend label (EX1030), which Helsinn emphasizes lacks statistical significance. *Supra*, Section XXXI.A.1.

1344. The ’826 patent data shows the aprepitant dose actually had ***improved*** anti-nausea effect compared to the lower of the netupitant doses (a comparably-sized day 1 dose as given for aprepitant). The independent claims of the ’826 patent do not require the 300 mg dose of netupitant. For example, while dependent claim 7 requires “300 mg of netupitant,” dependent claim 6 is even broader including “from about 200 to about 400 mg of netupitant.” EX1001 (’826 patent), claims 6-7. Independent claim 1 is broader still, not requiring a specific amount of netupitant. Data comparing the aprepitant dose to the lower netupitant doses is provided by the ’826 patent Table 6:

TABLE 6

SUMMARY OF SECONDARY EFFICACY
RESULTS: PERCENT OF PATIENTS, MFAS POPULATION

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No Rescue						
Overall	95.6	97.8	100	98.5	97.8	
Acute	97.8	99.3	100	100	100	
Delayed	97.1	97.8	100	98.5	97.8	
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59
Total Control						
Overall	50.0	54.8	61.3	59.3	56.0	
Acute	71.3	71.9	76.6	80.0	74.6	
Delayed	52.2	59.3	65.0*	65.9*	58.2	
Complete Protection						
Overall	69.9	76.3	80.3*	83.0*	78.4	51
Acute	87.5	89.6	88.3	97.0*	89.6	76
Delayed	73.5	80.0	87.6*	84.4*	82.1	66

*p-value < 0.05 compared with palonosetron-alone; aprepitant comparisons p-values calculated by post-hoc analysis
**As reported by Grunberg et al., Support Cancer Care (2009) 17: 589-594

EX1001 (’826 patent), Table 6. This data shows the aprepitant dose (blue) had similar antinausea effect to the 200 mg dose of netupitant (purple). Notably, the aprepitant dose had ***greater antinausea effect*** as compared to the 100 mg dose of netupitant (red). Thus, a POSA would have understood that the data shows aprepitant has an antinausea effect, that the effect is comparable to netupitant even

at the highest (300 mg) dose, and that the antinausea effect of aprepitant is better than low dose (100 mg) netupitant.

1345. The data presented in the "Palo + Aprep" column of the '826 patent Table 6 is not an apples-to-apples comparison with any of the other columns, and thus does not show any surprising results or particular benefit for using netupitant in the combination in place of aprepitant. Table 6 presents data from the patent's study evaluating netupitant-plus-dexamethasone-plus-palonosetron and juxtaposes it with data taken from a different study involving aprepitant-plus-dexamethasone-plus-palonosetron—Grunberg (EX1035). EX1001 ('826 patent), 5:2-5, 17:65-67. But the Grunberg study differed significantly and materially from the study in the specification. *See generally* EX1035 (Grunberg).

1346. First, the participants of Grunberg's study "could receive scheduled mildly or minimally emetogenic chemotherapy (Hesketh Level 1-2) during the remainder of the study period," which would cause additional emesis. EX1035 (Grunberg), 591. In contrast, the affidavit does not describe any additional emetogenic chemotherapy was permitted after the initial chemotherapy for any of the other comparators.

1347. Second, Grunberg did not administer the FDA-approved dose of aprepitant on Day 1 (125 mg). EX1013 (MASCC), Table 3; EX1016 (Herrington), 2081. Instead, Grunberg investigated the effect of administering a single large dose

of aprepitant, combining the doses of Day 1-3 into a single administration (285 mg) on Day 1. EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient single-day three-drug antiemetic regimen…. Prior to chemotherapy, patients received ***a single dose of aprepitant 285 mg*** p.o., dexamethasone 20 mg p.o., and palonosetron 0.25 mg i.v."). The affidavit's comparators fail to account for how such a large single dose of aprepitant might affect nausea and vomiting, such as whether adverse events (including nausea and vomiting) could arise. *See, e.g.*, EX1037 (Hesketh), 4116-4117 (nausea is an adverse event of aprepitant, but not evaluated as such until after 120 hours); EX1016 (Herrington), Abstract, 2084 (a ***single 125 mg*** dose of aprepitant effective for antiemesis).

1348. Third, Grunberg administered the antiemetic agent dexamethasone only in a single prophylactic dose on the first day prior to administration of the chemotherapeutic agent. EX1035 (Grunberg), 590-591 ("Patients received aprepitant 285 mg p.o. and ***dexamethasone 20 mg*** p.o. 1 h prior and palonosetron 0.25 mg i.v. 30 min prior to scheduled Day 1 chemotherapy."); *id.*, Abstract ("patients received ***a single dose of*** aprepitant…***dexamethasone***…and palonosetron"). In contrast, each of the specification's other study groups received the antiemetic dexamethasone administered on each of day one, day two, day three, ***and*** day four. EX1001, 17:19-64.

1349. Each of the above-described differences precludes making a direct comparison between Grunberg's results and the specification's results because such a flawed comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination.

1350. The differences between Grunberg's study and the studies detailed in the '826 patent are so significant that a POSA could not reasonably rely on comparing differences in outcomes to assert surprising or unexpected results. For example, the patent specification's flawed comparison of Grunberg's data to the specification's data is evidenced by the ***higher*** nausea observed in Grunberg for the combination of aprepitant-plus-dexamethasone-plus-palonosetron than what the specification reported for dexamethasone-plus-palonosetron ***without any NK_1 receptor antagonist***. EX1035 (Grunberg) (percentage of patients without particular measure of nausea: 32%, 59%, 41%, 56%, 79%, and 59%); EX1001 ('826 patent), Table 6 (50.7%, 75.0%, 53.7%, 79.4%, 93.4%, and 80.9%). The specification provides no reason to conclude that adding aprepitant to dexamethasone and palonosetron would reduce the efficacy of the dexamethasone and palonosetron. Indeed, such an assumption is contradicted by Grunberg's reports that, like prior studies of the antiemetic combination of aprepitant-plus-dexamethasone-plus-palonosetron "[e]xcellent control of nausea was also achieved" when Grunberg used this combination. EX1035 (Grunberg), 593.

1351. It is therefore my opinion that a POSA would not and could not have relied on the "Palo + Aprep" column of Table 6 of the '826 patent to assert any unexpected results as compared to the palonosetron and netupitant doses.

3. Campos

1352. Aprepitant was known to provide anti-nausea therapeutic effect during the acute period following administration of highly emetogenic chemotherapy. This is directly contrary to Helsinn's characterization of aprepitant in the patent specification, where Helsinn stated that "aprepitant's effect was limited principally to vomiting, ***not nausea***, and that aprepitant ***did not provide as much benefit during the acute phase*** [i.e., 0-24 hours] of CINV." EX1001 ('826 patent), 2:12-15.

1353. Campos discloses aprepitant's beneficial therapeutic effect for ***nausea*** and shows it provided significant additive benefit during the acute phase of CINV. Campos evaluated the effect of adding aprepitant (MK-869) to a 5-HT_3 receptor antagonist (granisetron) and dexamethasone. EX1023 (Campos), Abstract; *see* EX1011 (Hoffmann), 1362 (MK-869 is aprepitant). When NK_1 receptor antagonist aprepitant was added to Campos' 5-HT_3 receptor antagonist and dexamethasone, acute nausea decreased dramatically. EX1023 (Campos), 1763 & Table 4. Campos charts its data in Figure 2, reproduced below with highlighting added for the triple therapy combination including aprepitant.

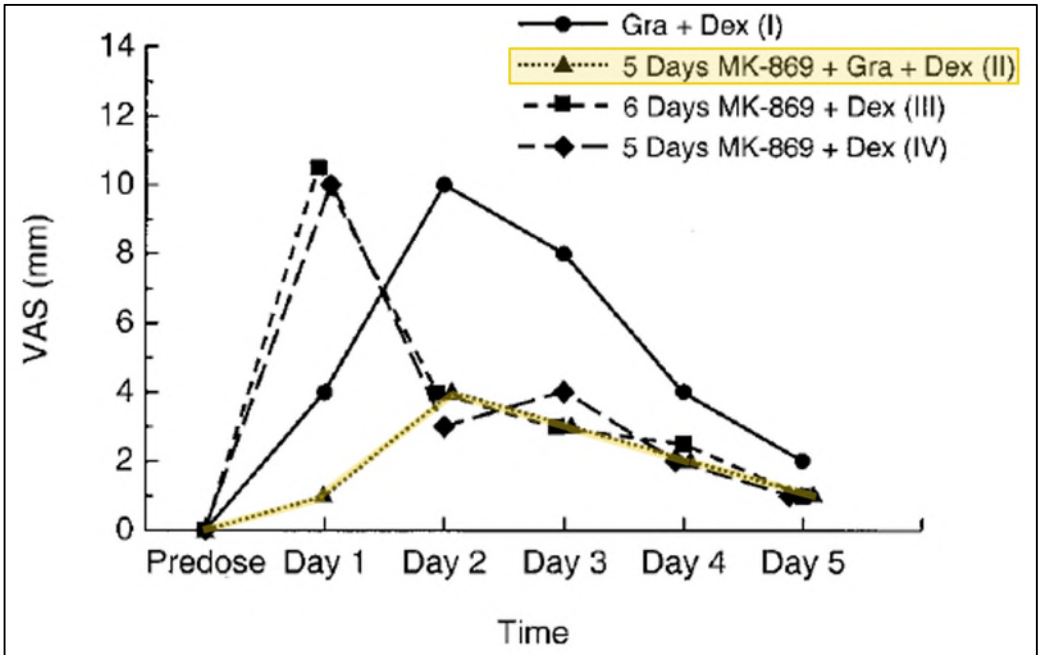


Fig 2. Median visual analog scale nausea scores over time irrespective of the use of rescue medication. Gra (granisetron) and Dex (dexamethasone) both administered on day 1 only. Groups I and II were significantly different when comparing the interval days 1 through 5, and days 2 through 5 ($P < .05$).

Id., Fig. 2. Campos explains that the triple therapy (5-HT_3 receptor antagonist, dexamethasone, plus aprepitant) provided "nausea ratings [that] were significantly lower" in "the first 24 hours rank analysis" compared to 5-HT_3 receptor antagonist plus dexamethasone. *Id.*, 1763. Campos also explains that median nausea scores were lower with the triple therapy in the delayed phase (days 2-5). *Id.*, 1763-1764.

1354. Thus, contrary to Helsinn's representations to the USPTO, aprepitant was known in the prior art to provide beneficial effect to nausea, including specifically providing therapeutic effect to prevent nausea during the acute phase for CINV.

4. Post-critical Publications

1355. I understand that within the confines of secondary considerations, reference may be made to post-critical publications. Studies that published after the critical date further show that aprepitant provides therapeutic efficacy for nausea, contrary to Patent Owner's contentions otherwise.

1356. For example, a study evaluating the efficacy of aprepitant with palonosetron and dexamethasone compared to placebo with palonosetron and dexamethasone found that "[t]he proportion of patients with ***no nausea or significant nausea*** in the overall phase was higher in the aprepitant vs placebo group (no nausea: 81 [65.9%] vs 59 [49.2%]; *P* = 0.08 [16.7-percentage point difference]; significant nausea: 121 [98.4%] vs 111 [92.5%]; *P* = 0.3 [5.9-percentage point difference." EX1047 (Wang), 6. Participants also filled out Functional Life Index-Emesis ("FLIE") questionnaires to evaluate negative influences following CINV, consisting of 9 questions relating to nausea and 9 questions relating to emesis. *Id.*, 3. "Quality of life in the aprepitant vs placebo group was significantly better according to the FLIE score" and specifically with regard to the "***nausea domain score*** (101 [82.1%] vs 76 [63.3%] [18.8-percentage point difference]; *P* = .001)." *Id.*, 6. Wang concludes that their study shows aprepitant "***had an important role in improving protection against nausea***." *Id.*, 8.

1357. A meta-analysis of 51 randomized controlled trials was conducted and also reported aprepitant had beneficial effect on nausea for patients receiving chemotherapy. EX1040 (Qiu), Abstract. Evaluating the data from over fifty trials, Qiu found that the aprepitant triple combination, compared to the standard combination, "significantly improved the proportion of patients who have no nausea event during the overall (OR 1.53, 95% CI 1.13 [-] 1.75, $P < 0.001$) and delayed phases (OR 1.50, 95% CI 1.30 – 1.74, $P > 0.001$)[.]" *Id.*, 3. In the meta-analysis, the acute phase showed improvement, but not significance. *Id.* The odds ratios ("OR") of the cumulative data of a multitude of studies evaluating aprepitant further evidenced that aprepitant confers a therapeutic benefit by decreasing nausea following chemotherapy.

1358. When compared to the prior art use of aprepitant in the triple-combination therapy, employing netupitant to treat both nausea and vomiting is thus not an unexpected result. The prior art clearly shows the prevention of both nausea and vomiting following chemotherapy by use of antiemetic drug combinations including the NK_1 receptor antagonist, aprepitant. The Emend label (EX1030) indicates that aprepitant has a beneficial effect on nausea and recent studies confirm it. Likewise the '826 patent itself illustrates ***benefits*** of aprepitant for treating nausea and shows the use of aprepitant provided results comparable to netupitant. Prior art and post-critical date studies also illustrate that aprepitant

provides beneficial therapeutic effect by reducing nausea. There was nothing surprising or unexpected by the NK_1 receptor antagonist netupitant having a similar effect to aprepitant.

1359. Insofar as there is any improvement for treating nausea using the triple therapy including netupitant that is not observed with the triple therapy including aprepitant, it is my opinion that the difference is not significant and not material—put differently, there is at most a difference of degree rather than a difference in kind. This is confirmed by the ’826 patent itself which shows, as I explained above, that the triple drug therapy including aprepitant performed substantially similar to the triple drug therapy including netupitant for treatment of nausea. *See, e.g.*, EX1001 (’826 patent), Table 6; *see also* EX1005 (file history of ’462 application), 346 (Declaration Table 2 (columns 1, 5, 8)) (reproduced below).

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Ondan + Aprep (HEC)[c1]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ns]	30.6	59.9[ns]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ns]	66.1	91[ns]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[nc1] Non-Comparative Study; statistical significance not evaluated

B. Misrepresentation of data during prosecution

1360. In response to the Office action rejecting claims for being obvious during prosecution of the application that issued as the ’826 patent, the applicant filed an Office action response as well as an affidavit. But the response that was submitted, which characterizes the affidavit and its underlying references, creates a false impression that there was more significant improvement with the triple therapy of netupitant, palonosetron, and dexamethasone than actually existed. This is shown partly by numerous differences between the information the applicant presented to the USPTO as compared to the information contained within the affidavit.

1. Differences between 1.312 Declaration and Applicant’s arguments

1361. The applicant argued to the USPTO that a POSA “would not have expected netupitant to successfully treat nausea because aprepitant – the only other NK_1 antagonist approved for CINV, and the NK_1 antagonist that allegedly supports the examiner’s prima facie case of obviousness – was ***unable to demonstrate a statistically significant effect on nausea*** in its clinical trials.” But as described above, this is false—the Emend label, the specifications’ own data, prior art, and post-critical date references all indicate there is substantial effect on nausea with aprepitant. *See* Sections XXXI.A.1-XXXI.A.4, above.

1362. The applicant then states to the USPTO that it is reproducing a "table [that] is taken from the 132 Declaration...filed concurrently herewith." But what the applicant presented to the USPTO was significantly and materially altered compared to the table in the 132 Declaration. Below I first reproduce, with annotations, the table the applicant presented to the USPTO, and then I produce, with annotations, the table from the 132 Declaration. Red highlights indicate cells where data differed from the declaration. Yellow highlights indicate removal of "not reported" values—which in some instances were simply deleted, but in others were presented instead as "not significant."

TABLE 2

	1	2	3	4	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
No Nausea								
Overall (0-120h)	61.5	58.2	50.3	ns	ns	32[nsc]	30.6[ns]	59.9[ncs]
Acute (0-24h)	80.0	77.6	ns	ns	ns			
Delayed (25-120h)	68.1*	60.4	ns	ns	ns			
No Significant Nausea								
Overall (0-120h)	89.6*	85.8	74.6*	ns	ns	56[ncs]	66.1[ns]	91[ncs]
Acute (0-24h)	98.5*	94.0	ns	ns	ns			
Delayed (25-120h)	90.4*	88.1	ns	ns	ns			

EX1005 (file history of '462 application), 331 (Response to the USPTO).

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[nc1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ns]	30.6	59.9[ns]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ns]	66.1	91[ns]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[nc1] Non-Comparative Study; statistical significance not evaluated

EX1005 (file history of '462 application), 346 (the declarants' representations to the USPTO).

1363. As I describe further below, it is my opinion that the removal of data gave the false impression that the combination of netupitant and palonosetron had a greater effect as compared to other drug combinations. *See* Section XXXI.B.2, below.

1364. Based on my experience, the actual data does not support the examiner's change in position. I can only surmise the examiner mistakenly attributed to the declaration what was actually described in the Office action response, and thus erred by believing there were unexpected and surprising results that did not exist.

2. Applicant's data presented to the USPTO was lacking

a. Internal Helsinn Studies (Columns 1-3)

1365. The examiner was never provided with underlying data for any palonosetron and netupitant combination. In support of its contention that palonosetron and netupitant provided surprising and unexpected results, the declarants relied on data purportedly from internal Helsinn studies. EX1005 (file history of '462 application), 346. Specifically, columns 1, 2, and 3 each purport to provide data from "Helsinn Study NETU-07-07" and "Helsinn Study NETU-08-18." *Id.* As I described above, I have reviewed the file history of the application and I understand two information disclosure statements were submitted, which provide references for the examiner to consider. I do not see either of these Helsinn studies in the information disclosure statement, nor do I see the studies anywhere in the file history.

1366. Thus, it would appear that the underlying data purporting to show a benefit of palonosetron and netupitant, as well as any other data contained in the studies, were withheld from the examiner's consideration. Insofar as the '826 patent specification provides numbers extracted from these two studies (*see* Section XXXI.A.2, above, discussing '826 patent Table 6), there is insufficient data provided to allow a POSA to scrutinize and compare the studies. In my

opinion, a POSA would not have compared the internal Helsinn netupitant studies without having an opportunity to review the (missing) underlying data.

b. Ondansetron + Aprepitant MEC Studies (Columns 4 and 7)

1367. The 132 Declaration excluded data from its summary presented to the examiner. To support its contention that there was no overall impact on nausea with ondansetron and aprepitant as compared to palonosetron and netupitant on mildly emetogenic chemotherapy, the Declaration included a summary of data from two studies. Certain data from those studies, which illustrated similar effect for ondansetron and aprepitant vs. netupitant and palonosetron, were excluded from the tables. Instead, the 132 Declaration falsely indicated the data was "not reported."

1368. Table 2 submitted in the 132 Declaration includes two columns concerning ondansetron and aprepitant for treatment of mildly emetogenic chemotherapy—columns 4 and 7. EX1005 (file history of '462 application), 346. The two studies from these columns are substantially similar and have identical dosing protocols. The data of column 4 comes from EX1034 (Warr), while the data of column 7 comes from Yeo (EX1048). The dosing protocol is summarized by EX1034 (Warr), Table 1 (reproduced below):

Table 1. Study Medication Schedule

Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
Aprepitant (n = 438)			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
Control (n = 428)			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

1369. The declarants of the 132 Declaration represented to the USPTO that the Yeo study did "not report" acute and delayed data. EX1005 (file history of '462 application), 346 (Declaration, Table 2 ("[nr] Data Not Reported")). This was false. Instead, excised data illustrates comparable effects to the palonosetron and netupitant combination for mildly emetogenic chemotherapy according to Helsinn's internal studies (column 3). Yeo reports that its aprepitant-based combination yielded 88.5% of patients that had no significant nausea during the acute period, and 74.1% of patients that had no significant nausea during the delayed phase. EX1048 (Yeo), Table 3. Yeo also reports that its aprepitant-based combination yielded 62.3% of patients that had no nausea during the acute period, and 47.3% of patients that had no nausea during the delayed phase. *Id.* I have updated the 132 Declaration Table 2 below to include these values.

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Ondan + Aprep (HEC)[c]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr 62.3	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr 47.3	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr 88.5	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr 74.1	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated

EX1005 (file history of '462 application), 346 (Declaration, Table 2). Comparing the aprepitant and ondansetron MEC data with the netupitant and palonosetron MEC data, the results are substantially similar, especially with prevention of significant nausea. Indeed, during the acute phase, there was a slight ***improvement*** in the aprepitant study as compared Helsinn's internal netupitant study.

1370. It is my opinion that the data withheld from the examiner's consideration further confirms that there were no unexpected results for the combination of netupitant and palonosetron. A POSA would have understood that the ondansetron studies only included the 5-HT_3 receptor antagonist in effective quantities during the acute phase (EX1048 (Yeo), Abstract) (half-life of

ondansetron being 4-6 hours; half-life of palonosetron being 38-40 hours (EX1010 (Herrstedt), Table 3)) and would have recognized that in this time period the netupitant study yielded equivalent results to the aprepitant study, particularly for prevention of significant nausea. A POSA would have considered any improvement with the netupitant dosing to be moderate at best—not unexpectedly beneficial or surprising.

c. FDA-Approved Prescribing Information for Emend (Column 4a)

1371. As I describe above, the Emend label supports that aprepitant prevents nausea for patients receiving highly emetogenic chemotherapy. *See* Section XXXI.A.1, above. The 132 Declaration does not include the "***complete protection***" data from the Emend label even though this parameter requires an evaluation of significant nausea.

1372. Table 2 of the 132 Declaration presented to the examiner during prosecution indicates data for acute phase of nausea and significant nausea was "not reported" EX1005 (file history of '462 application), 346 (Declaration Table 2, column 4a) but leaves unaddressed the Emend label's "***complete protection***" parameter which ***requires*** no significant nausea. *See* EX1030 (Emend label), 4 ("***complete protection*** (defined as no emetic episodes, no use of rescue therapy, and a maximum nausea visual analogue scale [VAS] score < 25 mm on a 0 to 100 mm scale)"). The Emend label summarizes two cohorts where aprepitant provided

statistically significant improvement for overall ***complete protection***. *Id.*, Table 1 (63% aprepitant compared to 49% standard), Table 2 (56% aprepitant compared to 41% standard). This benefit was also seen in the acute phase. *Id.*, Table 2 (80% aprepitant compared to 65% standard).

1373. Thus, it is my opinion that—contrary to the representations of the 132 Declaration—a POSA would have understood the Emend label to show a benefit against nausea—and in particular against significant nausea—when treating HEC with an aprepitant antiemetic drug combination. As I described above, the label illustrates an improvement for nausea parameters as well, though they were not calculated to statistical significance. The POSA would have understood that the ***complete protection*** value incorporated an evaluation of no significant nausea and was reported with statistical significance. I provide further details regarding this above. *See* Section XXXI.A.1, above.

d. Grunberg (Column 6)

1374. The ’826 patent contends that aprepitant and palonosetron “were far from promising” due to “the results reported in Grunberg.” EX1001 (’826 patent), 2:25-28 (citing EX1035 (Grunberg)). But both the ’826 patent and the 132 Declaration withheld from its summary presented to the examiner substantial and material differences in dosing across cohorts. The Declaration presents the Grunberg study (corresponding with data of Column 6) as though it is comparable

to the Helsinn internal studies, but there are significant differences between the studies that render them non-comparable.

1375. First, the participants of Grunberg's study "could receive scheduled mildly or minimally emetogenic chemotherapy (Hesketh Level 1-2) during the remainder of the study period," which would cause additional emesis. EX1035 (Grunberg), 591. In contrast, the affidavit does not describe any additional emetogenic chemotherapy was permitted after the initial chemotherapy for any of the Helsinn studies.

1376. Second, Grunberg did not administer the FDA-approved dose of aprepitant on Day 1 (125 mg). EX1013 (MASCC), Table 3; EX1016 (Herrington), 2081. Instead, Grunberg investigated the effect of administering a single large dose of aprepitant, combining the doses of Day 1-3 into a single administration (285 mg) on Day 1. EX1035 (Grunberg), Abstract ("The present study evaluated a more convenient single-day three-drug antiemetic regimen…. Prior to chemotherapy, patients received ***a single dose of aprepitant 285 mg*** p.o., dexamethasone 20 mg p.o., and palonosetron 0.25 mg i.v."). The affidavit fails to account for how such a large single dose of aprepitant might affect nausea and vomiting, such as whether adverse events (including nausea and vomiting) could arise. *See, e.g.*, EX1037 (Hesketh), 4116-4117 (nausea is an adverse event of aprepitant, but not evaluated

as such until after 120 hours); EX1016 (Herrington), Abstract, 2084 (a ***single 125 mg*** dose of aprepitant effective for antiemesis).

1377. Third, Grunberg administered the antiemetic agent dexamethasone only in a single prophylactic dose on the first day prior to administration of the chemotherapeutic agent. EX1035 (Grunberg), 590-591 ("Patients received aprepitant 285 mg p.o. and ***dexamethasone 20 mg*** p.o. 1 h prior and palonosetron 0.25 mg i.v. 30 min prior to scheduled Day 1 chemotherapy."); *id.*, Abstract ("patients received ***a single dose of*** aprepitant…***dexamethasone***…and palonosetron"). In contrast, each of the specification's other study groups received the antiemetic dexamethasone administered on each of day one, day two, day three, ***and*** day four. EX1001, 17:19-64.

1378. Each of these differences precludes making a direct comparison between Grunberg's results and the specification's results because such a flawed comparison would overstate the antiemetic effect of netupitant in the combination as compared to aprepitant in the combination.

1379. In view of the differences between the studies described above, the POSA would not have compared Grunberg's study with the Helsinn internal MEC study, and therefore it is my opinion that such a comparison cannot reasonably be relied upon to show any unexpected results.

C. No Unexpected Synergy Between Netupitant and Palonosetron

1380. The ’826 patent specification contends that “palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant” and “palonosetron shows an improved pharmacokinetic profile…in combination with netupitant as opposed to palonosetron in single dose administration.” EX1001 (’826 patent), 5:2-12. The 132 Declaration likewise argues that these are unexpected results and illustrate synergy. But as I explain below, there is no unexpected difference when compared to aprepitant and palonosetron.

1. No Defined Synergistic Effect

1381. I have reviewed the ’826 patent specification and did not find therein any definition or discussion regarding what constitutes “synergy” within the context of the claims or purported unexpected results. It is typically understood that synergy means that a combination has a greater benefit than the sum of its distinct parts.

2. No Unexpected Difference to Aprepitant and Palonosetron

1382. Even taking the values of the information presented in the 132 Declaration Table 2 at face value, a POSA would have understood this data to show the combination of palonosetron with *any* NK_1 receptor antagonist had a beneficial effect on nausea. Insofar as a synergistic effect existed, the declaration

data shows that such effect is just as applicable to the known combination of palonosetron and aprepitant.

1383. For example, the Declaration Table 2 shows that for highly emetogenic chemotherapy, palonosetron combined with netupitant yielded similar overall effects for no nausea and no significant nausea as palonosetron combined with aprepitant:

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Ondan + Aprep (HEC)[c1]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated

EX1005 (file history of '462 application), 346 (Declaration Table 2). A POSA accepting this data at face-value would have observed that palonosetron improved the significant nausea and nausea side effects of highly emetogenic chemotherapy with both NK_1 receptor antagonists—aprepitant and netupitant. The aprepitant

studies showed overall percentage of patients with ***no significant nausea*** at 88.5% and 91%, which are essentially equivalent to the netupitant study (89.6%). The percentage of aprepitant patients with no nausea overall (59.9%) was similar to the percentage of netupitant patients having no overall nausea (61.5%). Thus, there was no surprising or unexpected benefit of the netupitant and palonosetron combination.

1384. As described above, the applicant's version of the table submitted to the USPTO deletes the 88.5% value, marks it as "not significant," and ignored the 91% value. Section XXXI.B.1, above. But a POSA would not ignore the 91% value if one is to consider the bigger picture of NK_1 receptor antagonist activity: a POSA would have considered these results in the overall metric when considering whether netupitant and aprepitant conferred nearly the same anti-nausea effect overall. Netupitant did not provide any surprising results or synergy beyond what was observed with aprepitant.

1385. The data provided in the affidavit shows, at most, that palonosetron combined with *any* NK_1 receptor antagonist confers intrinsic benefit as compared to other 5-HT_3 receptor antagonists, but there is no unexpected and surprising synergy specific to the combination of palonosetron and netupitant. Reproduced below is Table 2 from the affidavit with annotations for the highly emetogenic

chemotherapy studies evaluating palonosetron (yellow) as the 5-HT_3 receptor antagonist as compared to ondansetron (green) as the 5-HT_3 receptor antagonist:

TABLE 2

	1	2	3	4	4a	5	6	7	8
Efficacy Endpoint	Palo + Netu (HEC)[a]	Ondan + Aprep (HEC)[a]	Palo + Netu (MEC)[b]	Ondan + Aprep (MEC)[c]	Ondan + Aprep (HEC)[c1]	Palo + Aprep (HEC)[d]	Palo + Aprep (MEC)[e]	Ondan + Aprep (MEC)[f]	Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated

EX1005 (file history of '462 application), 346 (Declaration Table 2). As can be seen from this table, palonosetron in combination with either aprepitant or netupitant showed equivalent results for percentage of patients with no significant nausea overall (89.6% (netupitant), 88.5% (aprepitant), 91% (aprepitant)). Similarly, palonosetron in combination with either NK_1 receptor antagonist showed equivalent results for percentage of patients with no nausea overall (61.5% (netupitant), 59.9% (aprepitant)). Any other differences between the studies were in my opinion marginal and insufficient to show unexpected or surprising results.

1386. Thus, I disagree with the declarants' statement that "we have observed an unanticipated statistically significant effect against nausea from the combination

of netupitant and palonosetron that has not previously been observed in clinical studies involving the combination of…aprepitant with palonosetron." EX1005 (file history of '462 application), 345. Even assuming as true that the data presented in Table 2 is accurate, the data at most indicates there is a benefit of combining palonosetron with aprepitant ***or*** netupitant because the underlying values for nausea show substantial similarity. A POSA would not have understood these data to show "an unanticipated statistically significant effect" specifically with the combination of netupitant and palonosetron.

D. Lack of nexus between alleged synergy and claimed effect

1387. I understand that the examiner allowed the application that issued as the '826 patent for a single reason: "132 Declaration, filed 5/17/2013, affiant showing evidence of synergy (unexpected result) from the combination of netupitant and palonosetron ***in regard to the claimed method***." EX1005 (file history of '462 application), 369. I do not agree that the declarants showed any evidence of synergy in a way that corresponds to the challenged claims.

1388. First, any benefit of palonosetron with an NK_1 receptor antagonist is an effect beyond the scope of the claims, which require netupitant. As I describe above, any benefit observed with the combination of netupitant and palonosetron is substantially the same as the combination of aprepitant and palonosetron. *See* Sections XXXI.A.1-XXXI.A.4, above. This data indicates, if anything, a benefit of

combining palonosetron and ***any*** NK_1 receptor antagonist. But patent applicant did not claim (and could not have claimed, because it was known in the prior art) palonosetron plus any other NK_1 receptor antagonist.

1389. Second, there is no dose requirement in most of the claims, and as I described above, aprepitant drug combinations were shown to be superior to low-dose netupitant drug combinations. *See* Section XXXI.A.2, above. In contrast, the studies showing alleged unexpected benefits that were presented to the USPTO specifically used a higher dose of netupitant. *Id.*; *see also* EX1001 (’826 patent), Table 6. But I understand the independent claims do not require such a dose, and therefore it is my opinion that any alleged unexpected results are not directed to the scope of the independent claims.

1390. Third, insofar as there is a synergistic inhibition of SP response in NC108-15 cells by the combination of netupitant and palonosetron (EX1005 (file history of ’462 application), 343-344 & Table 1), this only shows an in-vitro effect that POSA would not have understood necessarily showed an effect on nausea. As I described in the introduction, the inhibition of Substance P was a target for multiple therapeutic effects, including mood disorders and pain. Showing an in vitro increase of EC_{50} for the combination of netupitant and palonosetron fails to represent a measurement of nausea or vomiting. In vivo testing specifically evaluating nausea, as was later conducted in clinical trials would measure nausea.

As described above, those clinical trials showed there was no unexpected benefit with the combination of netupitant and palonosetron with respect to nausea. This is not unexpected because it was known in the field that "substance P may play a relatively more important role in the pathogenesis of vomiting than of nausea." (EX1034 (Warr), 2829). Thus, the alleged unexpected benefit from in vitro Substance P inhibition fails to have sufficient bearing on the claimed treatment of nausea.

E. Single Dose of Netupitant Not Unexpected

1391. During prosecution of the patent that issued as the '515 patent, the applicant argued that it was unexpected "that only a single dose of netupitant is required during the acute and delayed phases of emesis." EX1007 (file history of '327 application), 203. The '826 specification makes a similar claim. EX1001 ('826 patent), 4:38-42 ("unexpectedly been discovered…a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days"). I disagree.

1392. Herrington describes a single dose of aprepitant is sufficient for treatment of the acute and delayed phases of emesis. For example, Herrington shows substantively the same antiemetic response for participants receiving a single dose (125 mg on Day 1) of aprepitant compared to those receiving the FDA-approved 3-day aprepitant regimen (125 mg on Day 1; 80 mg on each of Days 2-

3). This was true both for the acute and the delayed phases of emesis. EX1016 (Herrington), Abstract, Table 3 (reproduced below).

TABLE 3
Proportion of Patients With No Emesis

	Percentage with no emesis				
	Arm A Palonosetron plus 3-day aprepitant, n = 28	Arm B Palonosetron plus 1-day aprepitant, n = 27	Asymptotic 95% CI*	P†	Arm C Palonosetron plus placebo, n = 16
Acute phase	96.4	100	(−10.5–3.3)	1.00	93.8
Delayed phase	92.9	92.6	(−13.5–14.0)	1.00	50.0
Both phases	92.9	92.6	(−13.5–14.0)	1.00	50.0

* Difference between 3-Day and 1-Day aprepitant.
† Fisher Exact test was used (3-Day vs 1-Day).

1393. Based on the results of Herrington, a skilled artisan would have expected a single dose of netupitant to also provide therapeutic effect during the acute and delayed phases of emesis. Additionally, as I describe above, netupitant was the new, second-generation NK_1 receptor antagonist and acted in the same mechanistic pathway as aprepitant to achieve the same therapeutic goal. The prior art recognized that aprepitant was merely the "the first of a new class of drugs" and a person having ordinary skill in the art would have considered it obvious to replace aprepitant with the second generation NK_1 receptor antagonists. EX1013 (MASCC), 22; EX1010 (Herrstedt), Abstract (aprepitant was merely "the first drug" in this class); *see, e.g.*, Sections VIII, XI.A, XII.A above. Hoffmann identified netupitant's favorable characteristics including high affinity and excellent oral activity as compared to other NK_1 receptor antagonists. EX1011

(Hoffmann), 1364. Hoffmann also noted that netupitant had excellent penetration into the central nervous system. *Id.* Hoffmann describes netupitant was among the moieties tested in vivo that were shown to potently inhibit NK1 agonist-induced foot tapping behavior in gerbils after oral administration. *Id.*, 1365. Bös also identified netupitant "is a potent and selective antagonist at recombinant human neurokinin, (NK1) receptors expressed in CHO cells" having high and selective affinity for NK_1 receptors. EX1014 (Bös), 18:42-48. Bös discloses numerous in vivo studies showing efficacy of netupitant. *Id.*, 18:64-19:9 (gerbils), 19:10-20 (ferrets), 19:21-25 (Suncus murinus). By administering netupitant to the subject before exposure to the emetogenic agent, netupitant "completely blocked the emesis induced by the emetogens." *Id.*, 19:10-20. Bös also noted that netupitant has a long half-life associated with increased receptor affinity. For example, in rats the terminal half-life was 24 hours, while "[i]n dogs the molecule had a half-life of 18 hours[.]" *Id.*, 19:31-37. In gerbils, the functional half-life was 30 hours. *Id.*, 18:64-19:10.

1394. The person having ordinary skill would have expected netupitant to work at least as effectively and in the same manner as aprepitant. Thus, the skilled artisan would have expected—since only a single dose of aprepitant was required for therapeutic effect during the acute and delayed phases of emesis—that only a

single dose of netupitant would also be required during the acute and delayed phases of emesis.

F. Acute Phase Treatment with Netupitant Not Unexpected

1395. During prosecution of the patent that issued as the ’515 patent, the applicant argued that it was unexpected “that netupitant also treats emesis during the acute phase” as well as delayed phase. EX1007 (file history of ’327 application), 203. I disagree.

1396. NK_1 receptor antagonists were known to treat emesis during the acute phase. For example, Herrstedt stated that “Aprepitant increases the effect of a serotonin$_3$-receptor antagonist plus a corticosteroid against ***acute emesis*** induced by highly or moderately emetogenic chemotherapy.” EX1010 (Herrstedt), Abstract. In other words, the addition of the NK_1 receptor antagonist aprepitant improved treatment of emesis during the acute phase. Similarly, Hargreaves reported that SP (NK_1 receptor) antagonists “were recently shown to block emesis in animal models and to ***prevent acute*** and delayed chemotherapy-induced ***nausea and vomiting*** (CINV) in the clinic.” EX1012 (Hargreaves), 18. MASCC guidelines recommended that “to prevent ***acute*** vomiting and nausea following chemotherapy of high emetic risk” one should administer the three-drug combination including NK_1 receptor antagonist. EX1013 (MASCC), 22. MASCC details a clinical study specifically concerning “the ***prevention of acute emesis*** induced by cisplatin

chemotherapy" and recognized the benefit of NK_1 receptor antagonist, aprepitant, in preventing said acute emesis. *Id.* Furthermore, as I explained above, Herrington describes a single dose of aprepitant is sufficient for treatment of ***the acute and delayed*** phases of emesis. Section IX.G, above.

1397. Thus, a skilled artisan would have expected netupitant to treat emesis during the acute phase as well as delayed phase. As I describe above, netupitant was a second generation NK_1 receptor antagonist and acted in the same mechanistic pathway as aprepitant to achieve the same therapeutic goal. *See* Section VIII, above. Aprepitant was merely the "the first of a new class of drugs" and a person having ordinary skill in the art would have understood it to be obvious to replace it with new NK_1 receptor antagonists. EX1013 (MASCC), 22; EX1010 (Herrstedt), Abstract (aprepitant was merely "the first drug" in this class). Netupitant had high potency, selective affinity for the NK_1 receptor, and excellent oral activity as compared to other NK_1 receptor antagonists. EX1011 (Hoffmann), 1364; EX1014 (Bös), 18:42-48. Hoffmann noted that netupitant had excellent penetration into the central nervous system. EX1011 (Hoffmann), 1364. Hoffmann also describes netupitant was among the moieties tested in vivo that were shown to potently inhibit NK1 agonist-induced foot tapping behavior in gerbils after oral administration. *Id.*, 1365. Bös also discloses numerous in vivo studies showing efficacy of netupitant. EX1014 (Bös), 18:64-19:9 (gerbils), 19:10-20 (ferrets),

19:21-25 (Suncus murinus). Netupitant "completely blocked the emesis induced by the emetogens." *Id.*, 19:10-20. Bös also noted that netupitant has a long half-life. *Id.*, 19:31-37 (24-30 hours). A person having ordinary skill would have expected netupitant to work at least as effectively and in the same manner. Thus, the skilled artisan would have also expected that netupitant treats emesis during the acute phase as well as delayed phase.

G. Characteristics of Netupitant Not Unexpected

1398. The '826 patent presents certain characteristics of netupitant—a compound that was known in the prior art—as allegedly unexpected. I disagree.

1399. The '826 specification states that:

> It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK_1 receptors in the brain. In particular, it has been discovered that netupitant binds to NK_1 receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK_1 receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

EX1001 ('826 patent), 4:37-51. But the purported unexpected discovery merely recites characteristics of netupitant itself. As I describe at length above, the

compound netupitant was already known in the field. *See* Sections IX.B, IX.C, above. The ’826 specification also recites:

> It has also been discovered that netupitant potentiates the effect of dexamethasone, such that the dexamethasone is effective even when administered at sub-therapeutic doses (i.e. doses at which the dexamethasone would be ineffective if administered by itself).

EX1001 (’826 patent), 5:13-20. But this again is a characteristic of netupitant—and of NK_1 receptor antagonists generally. As I explained above, the prior art showed that administration of dexamethasone is effective when administered at sub-therapeutic doses when co-administered with an NK_1 receptor antagonist, such as aprepitant. Section IX.E. Accordingly, it was not surprising or unexpected that netupitant provided the very same effect, and this is yet another characteristic of a known compound.

1400. It has been explained to me by counsel that a chemical composition and its properties are inseparable. Thus, if the prior art teaches the chemical at issue, the corresponding properties cannot be claimed. Each of the characteristics described above in the ’826 patent are properties of netupitant itself. EX1001 (’826 patent), 4:37-51. Because netupitant was already known in the prior art, any purported unexpectedness of netupitant’s characteristics cannot weigh in favor of patentability.

XXXII. CONCLUDING STATEMENTS

1401. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

1402. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 30 April, 2025

By: /Stephen J. Peroutka /
Stephen J. Peroutka , M.D., Ph.D.

XXXIII. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 8,623,826 B2, issued 17 January 2014
1002	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,186,357 B2, issued 17 November 2015
1003	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,943,515 B2, issued 17 April 2018
1004	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 10,828,297 B2, issued 10 November 2020
1005	Prosecution history for U.S. Appl. 13/077,462, filed 31 March 2011
1006	Prosecution history for U.S. Appl. 14/069,927, filed 01 November 2013
1007	Prosecution history for U.S. Appl. 15/003,327, filed 19 May 2016
1008	Prosecution history for U.S. Appl. 15/923,050, filed 16 March 2018
1009	*Intentionally left blank*
1010	J. Herrstedt & P. Dombernowsky, *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 Basic & Clinical Pharmacology & Toxicology 143-150 (2007)
1011	T. Hoffmann et al., *Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists*, 16 Bioorganic & Medicinal Chemistry Letters 1362-1365 (2006)

1012	R. Hargreaves, *Imaging Substance P Receptors (NK_1) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. Clinical Psychiatry 18-24 (2002)
1013	The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), *Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference*, 17 Annals of Oncology 20-28 (2006)
1014	M. Bös et al., *4-phenyl-pyridine derivatives*, U.S. Patent 6,297,375 B1 (issued 2 Oct. 2001)
1015	Eisai, Inc., ALOXI (palonosetron HCl) Capsules, package insert (Aug. 2008)
1016	J.D. Herrington et al., *Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting*, 112 Cancer 2080 (2008).
1017	D. Bonadeo et al., *Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability*, PCT Publication WO 2008/049552 (published 2 May 2008)
1018	R.J. Gralla et al., *Recommendations for the Use of Antiemetics: Evidence-Based, Clinical Practice Guidelines*, 17(9) Journal of Clinical Oncology 2971-2994 (1999).
1019	K. Jordan et al., *Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations*, 12 The Oncologist 1143-1150 (September 2007)
1020	Curriculum Vitae of Dr. Stephen J. Peroutka
1021	G.K. Reddy et al., *Novel Neurokinin-1 Antagonists as Antiemetics for the Treatment of Chemotherapy-Induced Emesis*, 3 Support Cancer Therapy 140-42 (2006).

1022	M.S. Aapro et al., *A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy*, 17 Annals of Oncology 1441-49 (2006)
1023	D. Campos et al., *Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone*, 19(6) Journal of Clinical Oncology, 1759 (2001)
1024	A.E. Chang et al., eds., Oncology: An Evidence-Based Approach (2006)
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1035	S.M. Grunberg et al., *Effectiveness of a single-day three-drug regimen of dexamethasone, palonosetron, and aprepitant for the prevention of acute and delayed nausea and vomiting caused by moderately emetogenic chemotherapy*, 17 Supportive Care in Cancer 589 (2009)
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1042	C. Ruhlmann & J. Herrstedt, *Casopitant: a novel NK1-receptor antagonist in the prevention of chemotherapy-induced nausea and vomiting*, 5 Therapeutics and Clinical Risk Management 375 (2009)

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1046	K.E. Thummel, *Gut instincts: CYP3A4 and intestinal drug metabolism*, 117(11) Journal of Clinical Investigation 3173 (2007)
1047	D.S. Wang, *Effect of aprepitant for the prevention of chemotherapy-induced nausea and vomiting in women: a randomized clinical trial*, 4(4) JAMA Network Open e215250 (2021)
1048	W. Yeo et al., *A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy*, 113 Breast Cancer Research and Treatment 529 (2009)
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