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. 9,186,357

DECLARATION OF RUDOLPH M. NAVARI, M.D., Ph.D., F.A.C.P.

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I, Rudolph M. Navari, M.D., Ph.D., F.A.C.P., declare as follows:

I. INTRODUCTION

1. I am hematologist oncologist and the Executive Director of the Cancer Care Program of Central and South America for the World Health Organization ("WHO"). The WHO program focuses on cancer prevention and control with implementation of evidence-based interventions for prevention, early detection diagnosis, treatment, and palliative care. I have practiced in the field of oncology for over 40 years. I still see patients five days a week and have treated over 200,000 patients throughout my career.

2. I have been retained by counsel for Helsinn Healthcare S.A. ("Helsinn" or "Patent Owner") in connection with this proceeding before the United States Patent and Trademark Office ("PTO"). I understand that this proceeding involves U.S. Patent No. 9,186,357 ("the '357 patent") (Ex. 1002).[1] I understand that the '357 patent is titled "Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting" and is presently owned by Helsinn.

3. I understand that Azurity Pharmaceuticals, Inc. ("Azurity" or "Petitioner") is challenging the patentability of claims 1-62 of the '357 patent

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[1] I understand that the documents I identify herein have been labeled with exhibit numbers, and I include those exhibit numbers here for ease of reference.

(collectively, "the challenged claims"). I also understand that Petitioner has submitted a declaration from Dr. Stephen J. Peroutka ("Peroutka Declaration") (Ex. 1009) in connection with Azurity's assertions regarding the challenged claims.

4. I have been asked to provide my opinions on, among other things, chemotherapy-induced nausea and vomiting ("CINV"), the '357 patent, the state of the art, and issues raised by Dr. Peroutka. For purposes of my opinions in this proceeding, I understand from counsel that the relevant time frame is the late 2000s, including the time leading up to November 18, 2009. This Declaration provides my opinions from the perspective of a person of ordinary skill in the art ("POSA") during that time frame.

5. Based on my review of the '357 patent, the state of the art, and other materials identified in Appendix A, I have arrived at the opinions and conclusions that are set forth in this Declaration. In preparing this Declaration, I relied on my own expertise, clinical experience, and knowledge of the literature in the field, including my background knowledge of supportive oncology.[2]

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[2] Supportive oncology (or supportive care in cancer) focuses on the prevention, control, and management of the adverse effects of cancer and its treatment to improve the quality of life for people living with cancer.

6. My opinions in this proceeding are based upon information currently known to me, and I may supplement or amend my opinions with respect to any additional information or opinions I become aware of after the date of the submission of this Declaration, including in response to any further declarations or opinions provided by Dr. Peroutka. As stated above, this Declaration contains responses to the statements, arguments, and conclusions contained in the Peroutka Declaration. It should also not be presumed that I agree with any specific statement, argument, or conclusion in the Peroutka Declaration unless I have addressed that conclusion or opinion herein.

7. I am being compensated for my work in this proceeding at my standard rate of $500/hour. My compensation is in no way contingent on the nature of my findings, the presentation of my findings in testimony, or the outcome of this or any other proceeding. I have no other interest in this proceeding.

II. BACKGROUND AND QUALIFICATIONS

8. I have been a practicing medical oncologist and cancer supportive care specialist since 1977. My clinical practice focuses on caring for patients with cancer and managing their symptoms, as guided by rigorous, evidence-based, collaborative research. My own research focuses on discovery, validation, and accessibility of innovative approaches to improving the quality of life of people

with cancer. A significant goal of my practice and research is to improve treatment tolerance and quality of life of patients with symptomatic cancer, including CINV.

9. I received an M.D. from the Medical College of Virginia in 1977. I also received a Ph.D. in Chemical Engineering from the University of Virginia in 1970, a M.S. in Chemical Engineering from University of Virginia in 1968, and a B.S. in Chemical Engineering from University of Notre Dame in 1966.

10. I completed my postdoctoral residency in internal medicine at the University of Alabama, Birmingham, where I was the Chief Resident (1977-1981). I completed a fellowship in medical oncology at the University of Washington and the Fred Hutchinson Cancer Research Center in Seattle Washington (1982-1983). I also later completed a fellowship in clinical medical ethics at the University of Chicago School of Medicine (1998-1999).

11. I have held medical licenses in Alabama, Washington, Indiana, Mississippi, and Missouri. I have received certifications from the American Board of Internal Medicine (1981) and the American Board of Internal Medicine in the Subspecialty Board of Medical Oncology (1983).

12. Throughout my work, I have been recognized as a key opinion leader in cancer supportive care research, including CINV. I have been involved in over 100 clinical trials, both national and local, and I am an author of over 150 published, peer-reviewed articles relating to symptom management and quality of

life for patients with cancer, including several specific to nausea and vomiting. I have also served in a consulting/advisory role for several pharmaceutical companies, including Merck, GSK, and Helsinn.

13. I have served as a member of every major guideline committee for antiemetics as well as for the treatment of solid tumors and hematological malignancies. The guidelines that I have helped develop include those provided by the National Comprehensive Care Network ("NCCN"), the Multinational Association of Supportive Care in Cancer ("MASCC"), and the American Society of Clinical Oncology ("ASCO"). These guidelines provide a consensus of expert views on currently accepted approaches to treating CINV. The creation of these guidelines and recommendations requires a comprehensive evaluation of the current CINV treatments as well as any recent developments.

14. I have also served as a member of various professional and honorary societies, as well as a reviewer on editorial boards. These include *Current Drug Targets*, *Expert Review of Quality of Life in Cancer Care*, and *Cancer Management and Research*.

15. My qualifications, professional experience, education, patents, and publications are set forth in my *curriculum vitae*, which is being submitted as Ex. 2044.

III. MATERIALS REVIEWED

16. In forming my opinions expressed in this Declaration, I reviewed and considered the materials cited in this Declaration as well as the materials listed in Appendix A. All of the opinions contained in this Declaration are based on the documents I reviewed, as well as my professional judgment, education, and knowledge and experience regarding oncology and supportive cancer care medications.

17. My opinions are also guided by my appreciation of what a POSA (as that term is defined below) would have understood about the state of the art during the relevant time period (late 2000s, including the time leading up to November 18, 2009). I understand that this time frame is based on the November 18, 2009 filing date of U.S. Provisional Application No. 61/262,470, to which the ’357 patent claims priority.

IV. LEVEL OF ORDINARY SKILL

18. Counsel has asked me to provide my opinions in this Declaration from the perspective of a POSA with respect to the ’357 patent as of the relevant time period as defined above in Paragraph 4. I further understand that the POSA is presumed to be aware of all the pertinent prior art. In my opinion, the relevant field of invention is oncology and, more specifically, supportive cancer care.

Supportive cancer care is, in general, the prevention, control, and management of the adverse effects of cancer and its treatment.

19. In my opinion, a POSA in November 2009 was actively involved in the field of oncology and, more specifically, supportive cancer care, which involves a number of disciplines and requires collaborative teamwork among persons with relevant experience. The POSA could have an advanced degree (*e.g.*, Ph.D., M.D., M.S., MSN, DNP, or equivalent) in a relevant field (*e.g.*, oncology) with at least three years of experience in oncology, including the treatment of nausea and vomiting with supportive cancer care medications in cancer patients undergoing chemotherapy. In this definition of a POSA, more education can substitute for less practical experience, and vice versa.

20. I provide this definition of a POSA based on my review of the '357 patent, the technology, the educational level and experience of active workers in the field, the types of problems faced by workers in the field, the solutions found to those problems, the sophistication of the technology in the field, and drawing on my own experience.

21. I understand that Dr. Peroutka proposes a different definition of a POSA. Under Dr. Peroutka's definition, a POSA did not need to have experience in oncology. (Ex. 1009 at ¶¶ 59-60.) I disagree with Dr. Peroutka's definition. Dr. Peroutka's definition is not directed to the subject matter of the invention,

which is supportive care in oncology, particularly methods of treating or preventing both nausea and vomiting in patients undergoing chemotherapy. My opinions in this case, however, are the same regardless of which definition for a POSA is adopted.

22. I believe I am an expert in the field of oncology and supportive cancer care. Over the course of my career, I have instructed numerous students and supervised many clinicians who were junior to me. My interactions with these individuals helped me to analyze the questions posed in this proceeding from the perspective of a hypothetical POSA, who would have had less experience than I.

V. STATE OF THE ART AT THE TIME OF THE INVENTION

A. Chemotherapy-Induced Nausea and Vomiting

23. "Chemotherapy" is a systemic type of drug therapy that uses chemicals to kill fast-growing cells, like cancer. Despite often being referred to as a single adverse event associated with cancer treatment, the phrase "chemotherapy-induced nausea and vomiting" (or "CINV") actually encompasses two separate adverse events that may be induced by chemotherapy: (1) nausea, and (2) vomiting. (*See, e.g.*, Ex. 2036 at 517, 528; Ex. 1010 at 143 ("Nausea and vomiting are ranked by patients as two of the worst adverse effects of cancer chemotherapy.").) "Nausea" is a difficult term to put into words but is usually considered a sick or queasy sensation that is perceived as being in the stomach, and

is sometimes followed by vomiting. (Ex. 2036 at 517.) "Vomiting" (also known as "emesis")[3] may consist of a pre-ejection phase (called "retching") followed by ejection of stomach contents. (Ex. 2036 at 517.) The sensation of nausea and the act of vomiting are protective reflexes with overlapping but distinct physiological pathways that work together to rid the intestine and stomach of toxic substances. (Ex. 2036 at 517.) Notably, nausea and vomiting do not always coexist simultaneously, as one can experience nausea without vomiting, and one can also suddenly vomit without nausea. (Ex. 2036 at 517.)

24. CINV results in significant morbidity and negatively affects the quality of life of cancer patients. (Ex. 2036 at 516; Ex. 2001 at 1856; Ex. 1019 at 1144; Ex. 2037 at 572.) CINV can result in weakness, weight loss, electrolyte imbalance, dehydration, and anorexia, and is associated with a variety of other complications, including fractures, esophageal tears, decline in behavioral and mental status, and wound dehiscence. (Ex. 2036 at 516; Ex. 2001 at 1856; Ex. 2037 at 572.) Consequently, CINV may result in non-adherence to, dose

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[3] When I use the term "emesis," I am referring to the acts of retching (dry heaving) or vomiting (expulsion of stomach contents), which do not include nausea.

reductions in, or even withdrawal from chemotherapy treatments for treatable cancers with positive historical clinical outcomes. (Ex. 2036 at 516; Ex. 1019 at 1144 ("Twenty years ago, nausea and vomiting were common adverse events of certain types of chemotherapy and forced up to 20% of patients to postpone or refuse potentially curative treatment."); Ex. 2001 at 1856; Ex. 2037 at 572.) While approximately 70% to 80% of all patients undergoing chemotherapy experience nausea and/or vomiting, patients tend to experience nausea more frequently than vomiting. (Ex. 2037 at 573.)

25. Historically, chemotherapeutic agents were believed to cause CINV by activating certain neuroreceptors located in the central nervous system, brain, and gastrointestinal tract. (Ex. 2037 at 573; Ex. 2036 at 517.) Various neuroreceptors have been identified as potentially being involved in CINV, including serotonin receptors, dopamine receptors, neurokinin-1 (NK-1) receptors, acetylcholine receptors, GABA receptors, histamine receptors, cannabinoid receptors, opiate receptors, endorphin receptors, and muscarinic receptors. (Ex. 2036 at 517-18; Ex. 2037 at 573.) Some exemplary agents include benzodiazepines, cannabinoids, corticosteroids, dopamine antagonists, neurokinin-1 receptor antagonists ("NK-1 receptor antagonists"), and serotonin 5-HT_3 receptor antagonists ("5-HT_3 receptor antagonists"). (Ex. 2001 at 1872 (Table XII).)

26. Chemotherapeutic agents are classified by their emetic risk, such as high emetogenic chemotherapy ("HEC") with a >90% risk of emesis, moderate emetogenic chemotherapy ("MEC") with a 30-90% risk of emesis, low emetogenic chemotherapy with a 10-30% risk of emesis, and minimal emetogenic chemotherapy with a 0-10% risk of emesis. (Ex. 2037 at 585; Ex. 1019 at 1144.)

27. The drugs that are used to treat CINV are administered prophylactically, meaning they are given to patients in advance of chemotherapy in an effort to prevent chemotherapy-related adverse events. An antiemetic therapy's control of CINV has typically been measured in three phases following the administration of chemotherapy: acute (0-24 hours), delayed (>24-120 hours), and overall (0-120 hours).[4] (Ex. 2037 at 585-86; Ex. 2001 at 1860.) Antiemetic

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[4] If despite prophylactic treatment, patients still experience vomiting and/or nausea within five days after chemotherapy administration, this condition is referred to as "breakthrough" CINV and would require "rescue therapy" treatment with additional antiemetics. (Ex. 2037 at 585.) Because "[i]t is very unlikely that established nausea and vomiting will respond to an agent in the same drug class after unsuccessful prophylaxis with an agent with the same mechanism of action,"

combinations are specifically chosen depending on their efficacy during these different time periods. (Ex. 2037 at 585-86; Ex. 2036 at 525-26.)

28. As part of the process of developing potential treatments for CINV, a scientist will conduct clinical trials in humans to evaluate whether the test drug candidate shows efficacy in treating CINV. In these trials, control of vomiting and nausea must be measured independently across the acute period, the delayed period, and the overall period. (*See* Ex. 2001 at 1860, Table IV.) However, in November 2009, composite endpoints that represent various combinations of vomiting, nausea, both nausea and vomiting, or the use of rescue medications, were used to assess the efficacy of a given drug candidate, resulting in confusion about whether nausea and/or vomiting were being controlled. (*See* Ex. 2001 at 1860, Table IV.)

29. In general, the use of composite endpoints in clinical studies attempts to summarize the patient's experience of CINV as a single endpoint. The following composite endpoints are some examples that were used in clinical studies in November 2009 to assess the efficacy of a given drug candidate:

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rescue therapy typically involves different drugs than were used prophylactically. (Ex. 2036 at 526.)

- **Total Control** = no vomiting, no use of rescue antiemetics, and no nausea
- **Complete Protection** or **Complete Control** = no vomiting, no use of rescue antiemetics, and no significant nausea
- **Complete Response** = no vomiting and no use of rescue antiemetics

(*See* Ex. 1048 at 531; Ex. 2001 at 1860, Table IV; Ex. 1022 at 1442.)

30. "Complete response" is the primary endpoint most often relied upon to demonstrate efficacy in clinical trials for CINV regimens, including by the FDA in connection with evaluating a drug product for potential approval. The "complete response" endpoint, however, excludes nausea as a parameter and only measures the ability to control vomiting. (Ex. 2036 at 521-22.) As a result, drugs or drug regimens that failed to adequately control nausea in a significant number of patients still received approval for indications for the prevention of CINV. (Ex. 2036 at 528; Ex. 1010 at 143.)

B. As of November 2009, FDA-Approved CINV Treatments Did Not Allow for Adequate Control of Nausea

31. Prior to the use of "triple therapy" (a term I explain below) in the treatment of CINV, clinicians used "standard therapy," which was a two-drug

regimen involving dexamethasone and a 5-HT_3 receptor antagonist.[5] (Ex. 2036 at 521.) By November 2009, the treatment guidelines for the prevention of CINV had evolved to recommend administration of a three-drug regimen that combined dexamethasone, a 5-HT_3 receptor antagonist, and aprepitant. This combination was referred to as "triple therapy," where each drug belongs to a different class and has a unique mechanism of action within that combination: (1) a corticosteroid (*e.g.*, dexamethasone), (2) a 5-HT_3 receptor antagonist (*e.g.*, palonosetron), and (3) the NK-1 receptor antagonist aprepitant. (Ex. 2036 at 521.)

32. Aprepitant's inclusion in triple therapy improved the control of acute and delayed emesis compared to standard therapy (5-HT_3 receptor antagonist and dexamethasone). (Ex. 2036 at 521.) However, despite being useful in the control of emesis, the "control of nausea was not improved with the use of aprepitant." (Ex. 2036 at 522, 527 ("Aprepitant did not improve nausea in the study.").)

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[5] An "antagonist" is a chemical compound administered to block other molecules from binding to their receptors. (Ex. 1010 at 144.) For example, a chemical compound that blocks or inhibits another molecule from binding to an NK-1 receptor is referred to as an "NK-1 receptor antagonist."

33. Below, I briefly discuss what was known by November 2009 about each drug class that is included in "triple therapy" and its respective mechanism of action.

1. Corticosteroids

34. The first drug class in triple therapy to have been recognized as useful for treating CINV was corticosteroids. The recommended corticosteroid for use in triple therapy was dexamethasone, in large part due to its widespread use. (Ex. 1010 at 145.)

35. A number of studies had shown that for patients receiving moderately or highly emetogenic chemotherapy, dexamethasone prevented both acute and delayed vomiting. (Ex. 2036 at 524; Ex. 1010 at 145.) While studies had determined the optimal pre-chemotherapy dosages, the optimal dose for the control of delayed emesis had not been determined. (Ex. 2036 at 524.)

2. 5-HT_3 Receptor Antagonists

36. The second drug class in triple therapy to have been recognized as useful for treating CINV was 5-HT_3 receptors antagonists. 5-HT_3 receptors antagonists were believed to be effective in preventing acute vomiting because they blocked the serotonin receptors that typically react to serotonin rapidly released from the gut in response to the cytotoxic agents of chemotherapy. (Ex. 2036 at 518-19; Ex. 1010 at 144.)

37. After the discovery of 5-HT_3 receptors antagonists, but before NK-1 receptor antagonists started being used to treat CINV, the published CINV treatment guidelines recommended the use of a 5-HT_3 receptor antagonist and dexamethasone pre-chemotherapy (*i.e.*, day 1) for the prevention of acute chemotherapy-induced vomiting, and the use of dexamethasone with or without a 5-HT_3 receptor antagonist following chemotherapy (days 2–4) for the prevention of delayed chemotherapy-induced vomiting. (Ex. 2036 at 518-19.)

38. The guidelines recommend the following 5-HT_3 receptor antagonists for use in triple therapy: dolasetron, granisetron, ondansetron, tropisetron, azasetron, ramosetron, and palonosetron. (Ex. 2036 at 519.)

3. Neurokinin-1 Receptor Antagonists

39. The third drug class in triple therapy was NK-1 receptor antagonists. The NK-1 receptor antagonist recommended by the guidelines was aprepitant.[6]

40. As of 2009, clinical studies had demonstrated that for patients receiving MEC or HEC, NK-1 receptor antagonists improved the control of

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[6] Aprepitant had two formulations, oral tablets of aprepitant marketed under the brand name Emend® and an injectable prodrug of aprepitant (fosaprepitant

delayed emesis, but did not have a significant effect on the control of acute emesis or any phase of nausea. (Ex. 1034 at 2826 ("There were significant differences favoring aprepitant in the vomiting domain score (85.7% v 71.8%; P < .001) . . . but not in the nausea domain score (53.5% v 50.5%)."), 2827 ("There were no significant differences between the two treatment groups in reports of overall nausea (VAS < 5 mm; 33% for both) or significant nausea (VAS < 25 mm; aprepitant 61%, control 56%)."), 2828-29 ("In the present study, the most pronounced effect of aprepitant was seen in the prevention of vomiting, with an absolute difference of 17% between the aprepitant regimen and the control group. . . . There was no significant effect of aprepitant on nausea."); Ex. 1048 at 532-34.) For example, as of 2009, it was believed that "use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, while there was no difference in the nausea domain." (Ex. 1048 at 534.)

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dimeglumine), which was marketed as Emend® for Injection ("Emend® IV"). (Ex. 2002; Ex. 2004.) When fosaprepitant is administered intravenously, it is converted to aprepitant within 30 minutes after administration and provides a similar antiemetic effect. (Ex. 2036 at 522.)

41. In November 2009, numerous NK-1 receptor antagonists were under investigation or had been investigated, including but not limited to the following compounds:

- ZD4974 (developed by AstraZeneca) (Ex. 2045)
- CGP49823 (developed by Ciba-Geigy) (Ex. 2046)
- Lanepitant (developed by Eli Lilly) (Ex. 2047)
- LY686017 (developed by Eli Lilly) (Ex. 2048)
- FK888 (developed by Fujisawa) (Ex. 2049)
- Vofopitant (developed by GlaxoSmithKline) (Ex. 2050)
- Vestipitant (developed by GlaxoSmithKline) (Ex. 2051)
- Orvepitant (developed by GlaxoSmithKline) (Ex. 2057)
- Befetupitant (developed by Hoffmann-La Roche) (Ex. 1011)
- R116031 (developed by Janssen) (Ex. 2066)
- L-733060 (developed by Merck) (Ex. 2052)
- L-736281 (developed by Merck) (Ex. 2053)
- TKA731 (developed by Novartis) (Ex. 2054)
- NKP608 (developed by Novartis) (Ex. 2055)
- CP-99994 (developed by Pfizer) (Ex. 2056)
- CP-122721 (developed by Pfizer) (Ex. 2050)

- CJ-17493 (developed by Pfizer) (Ex. 2058)
- CJ-11974 (developed by Pfizer) (Ex. 2050)
- CJ-11972 (developed by Pfizer) (Ex. 2059)
- RP67580 (developed by Rhone-Poulenc Rorer) (Ex. 2060)
- Dapitant (developed by Rhone-Poulenc Rorer) (Ex. 2061)
- SSR240600 (developed by Sanofi-Aventis) (Ex. 2062)
- SCH388714 (developed by Schering-Plough) (Ex. 2063)
- Rolapitant (developed by Schering-Plough) (Ex. 2051)
- TAK637 (developed by Takeda) (Ex. 2061)
- HSP117 (developed by Hisamitsu) (Ex. 2056)
- KRP103 (developed by Kyorin Pharm) (Ex. 2064)
- SLV317 (developed by Solvay) (Ex. 2065)

(*See* Ex. 2045-Ex. 2066; *see also* Ex. 1001 at 3:24-43; Ex. 2001 at 1873; Ex. 2036 at 519.)

C. In 2009, Various Drug Candidates Showed Potential for Controlling Chemotherapy-Induced Nausea

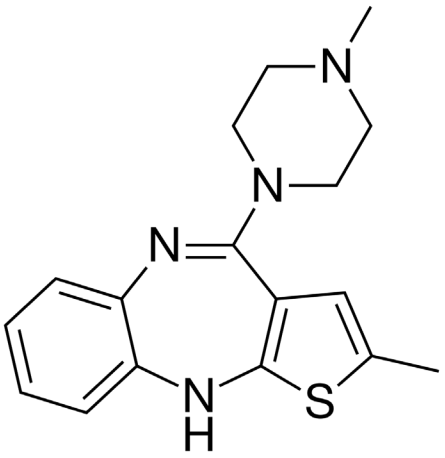
42. As of 2009, the gold-standard triple therapy had largely solved the problem chemotherapy-induced vomiting (emesis), but not chemotherapy-induced nausea, meaning that a majority of patients still experienced nausea following chemotherapy. (Ex. 1010 at 143, 148; Ex. 2036 at 528.) At that time, numerous

large clinical studies suggested that, while NK-1 receptor antagonists (*e.g.*, aprepitant) and 5-HT_3 receptor antagonists (*e.g.*, ondansetron, palonosetron) with dexamethasone significantly improved the prevention of vomiting, they had no significant effect on the control of nausea. (*See, e.g.*, Ex. 2036 at 527-29; Ex. 1034 at 2826-29; Ex. 1022 at 1444-46; Ex. 1048 at 531-34.) As a result, and unlike chemotherapy-induced vomiting, the control of nausea in patients receiving moderately and highly emetogenic chemotherapy remained a significant problem. (Ex. 2036 at 528; Ex. 1010 at 143 ("the majority of patients consider[ed] nausea as the main problem"), 148 ("Nausea and loss of appetite are the main problems for the majority of patients."); Ex. 2037 at 573 ("patients often experience more nausea than vomiting"); Ex. 1034 at 2826-29; Ex. 1022 at 1444-46; Ex. 1048 at 531-34.).)

43. Notwithstanding this, as of November 2009, numerous drug candidates had demonstrated promising antinausea efficacy in the treatment of CINV. Below, I discuss some exemplary compounds that were considered promising candidates at that time.

1. Olanzapine

44. Olanzapine is an FDA-approved antipsychotic that received approval for schizophrenia in 1996. The structure of the compound is below:



Olanzapine blocks multiple receptors including "dopamine at D1, D2, D3 and D4 brain receptors, serotonin at 5-HT2a, 5-HT2c, 5-HT3 and 5-HT6 receptors, catecholamines at a1-adrenergic receptors, acetylcholine at muscarinic receptors and histamine at H1 receptors." (Ex. 2036 at 524.)

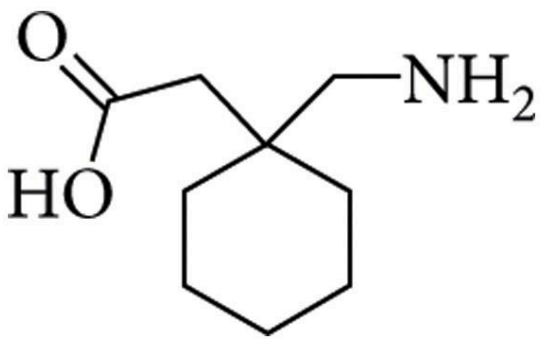
45. In 2009, a POSA would have understood that olanzapine in combination with a 5-HT_3 receptor antagonist and dexamethasone "***showed promise in controlling acute and delayed nausea*** in patients receiving moderately and highly emetogenic chemotherapy." (Ex. 2036 at 528 (emphasis added); *see also* Ex. 1019 at 1149 ("Olanzapine, an atypical antipsychotic drug, has potential antiemetic properties because of its action at multiple receptor sites implicated in the control of nausea and vomiting."); Ex. 1010 at 149 ("The most promising

seems to be olanzapine with very high complete response rates of both nausea and vomiting, when combined with a 5-HT3-receptor antagonist and a corticosteroid."); Ex. 2037 at 588 ("studies have also shown the value of olanzapine for delayed and refractory emesis and nausea").)

46. In fact, subsequent further research that I conducted after 2009, including human clinical studies, confirmed that olanzapine could potentially allow for control of nausea as part of a treatment for CINV. Specifically, my studies showed that, when added to triple therapy, olanzapine "significantly improved nausea prevention, as well as the complete-response rate" in patients receiving highly emetogenic chemotherapy. (Ex. 2039 at 134.) For example, in a Phase III trial conducted in 2016, we compared the combination of olanzapine plus triple therapy (*i.e.*, olanzapine plus dexamethasone, aprepitant, and palonosetron) to triple therapy alone. (Ex. 2039 at 134.) We found that the "proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine." (Ex. 2039 at 134.) In the first 24 hours after chemotherapy, 74% of patients experienced "no nausea" using olanzapine plus triple therapy, as compared to 45% of patients experiencing "no nausea" when triple therapy alone was used. (Ex. 2039 at 134.)

2. Gabapentin

47. Gabapentin is an FDA-approved antiepileptic drug approved for the prevention and control of partial seizures (convulsions) in the treatment of epilepsy. The structure of the gabapentin is below:



48. By 2009, a POSA would have known that a study with patients receiving HEC for breast cancer was conducted and "suggested that the anti-epileptic gabapentin may reduce delayed nausea," but noted that "[f]urther studies will be necessary to determine the efficacy of this agent." (Ex. 2036 at 525; *see also* Ex. 1010 at 149.)

3. Cannabinoids

49. Cannabinoids are class of biological compounds that bind to cannabinoid receptors. The chemical is sourced from plants of the cannabis genus (*e.g.*, marijuana plants).

50. By 2009, two oral formulations of cannabinoids (dronabinol and nabilone) had been approved by the FDA for use in CINV. (Ex. 2036 at 525.) In

"a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, it was found that cannabinoids were slightly better than conventional antiemetics (e.g., metoclopramide, phenothiazines, haloperidol)." (Ex. 1019 at 1147.) The NCCN guidelines had suggested the use of cannabinoids for breakthrough treatment and recent evidence had indicated that CB2 receptors may have a role in controlling emesis and/or nausea. (Ex. 2036 at 525; Ex. 2037 at 589-90.) In 2009, a POSA would have thought that cannabinoids may be useful in the control of chemotherapy-induced nausea based on their mechanism of action. (Ex. 2036 at 528.)

D. The '357 Patent Offered a Much-Needed CINV Treatment That Allowed for Control of Nausea

51. In my opinion, the '357 patent describes an improved CINV treatment that was also effective against nausea and represented a significant and much-needed advance in supportive care for cancer patients undergoing chemotherapy. The specification of the '357 patent indicates that after "extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active ***against nausea***, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days." (Ex. 1002 at 4:35-42 (emphasis added).)

52. The inventors further discovered that a drug regimen including a combination of netupitant and palonosetron provided "an unanticipated statistically significant effect ***against nausea*** . . . that [had] not previously been observed in clinical studies" of other NK-1 receptor antagonists in combination with other 5-HT_3 inhibitors. (Ex. 1005 at 345, ¶ 28 (emphasis added).)

53. The '357 patent further observes that when the chemical compounds of netupitant (an NK-1 receptor antagonist) and palonosetron (a 5-HT_3 receptor antagonist) are administered together, this produces unexpected synergistic effects "result[ing] in even greater efficacy against nausea." (Ex. 1001 at 4:65-5:12.)

54. During prosecution of the first patent in the family, U.S. Patent No. 8,623,826, Helsinn submitted a Rule 132 declaration explaining the unexpected synergistic effects of the netupitant-palonosetron combination in inhibiting substance P response.[7] (*See* Ex. 1005 at 334-338 (Helsinn's Remarks on synergistic effects, citing the Rule 132 declaration).) The Rule 132 declaration explained that the synergistic effects of this combination of palonosetron and

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[7] Substance P is a naturally occurring substance in the body that binds to NK-1 receptors. (Ex. 1010 at 146; Ex. 1005 at 342, ¶ 12.)

netupitant on substance P ***inhibition*** was greater than the additive effects of netupitant and palonosetron when administered separately.

55. The Rule 132 declaration provided the following table describing the EC_{50} value of substance P in several experiments performed by Helsinn:[8]

TABLE 1

Inhibition of SP response in NG108-15 cells by netupitant (netu) and palonosetron (palo).

SP + Antagonist(s)	EC_{50} (μM) ± S.E.M.	n
SP only	2 ± 0.2	38
Plus netu (1 nM)	2 ± 0.3	3
Plus netu (3 nM)	5 ± 3	3
Plus netu (10 nM)	10 ± 0.9	3
Plus netu (30 nM)	40 ± 10[a]	6
Plus palo (0.2 nM)	2 ± 0.1	3
Plus palo (0.6 nM)	3 ± 0.6	3
Plus palo (2 nM)	10 ± 2	3
Plus palo (6 nM)	30 ± 6[a]	5
Plus net (1 nM) plus palo (0.2 nM)	120 ± 20[b]	7
Plus net (30 nM) plus palo (6 nM)	970 ± 150[c]	5

(Ex. 1005 at 343, ¶ 17.)

56. As shown in Table 1, netupitant at a concentration of 1 nM did not exhibit any effect on substance P response, but at concentrations of 3 nM, 10 nM, and 30 nM of netupitant, there was an increase in the effect on substance P

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[8] An EC_{50} value is used to quantify the relationship between the concentration of a substance and the biological response elicited by that substance.

response. (Ex. 1005 at 343, ¶ 18.) At a concentration of 30 nM of netupitant, the maximum inhibition of substance P response for netupitant alone was observed, as reflected by the highest EC_{50} value. (Ex. 1005 at 343, ¶ 18.) Similarly, palonosetron at a concentration of 0.2 nM had no effect on substance P response. (Ex. 1005 at 343, ¶ 19.) However, at concentrations of 0.6 nM, 2 nM, and 6 nM of palonosetron, there was a corresponding increase in substance P response with a maximum inhibition at 6 nM for palonosetron alone. (Ex. 1005 at 343, ¶ 19.)

57. But when the inventors combined netupitant and palonosetron, even at concentrations where neither individual compound increased the EC_{50} of substance P when administered alone, the combination increased the EC_{50} of substance P from 2 μM to 120 μM. This value was a ***60-fold*** increase in the EC_{50} of substance P, whereas the additive increase should have been zero.[9] (Ex. 1005 at 343, ¶ 21.) Additionally, when a combination of 30 nM netupitant and 2 nM palonosetron was administered together, there was a nearly ***500-fold*** increase to 970 μM. (Ex. 1005 at 343, ¶¶ 22-23.) This exponential increase was very

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[9] The "μM" values represent the "EC_{50}" of substance P. An EC_{50} value is used to quantify the relationship between the concentration of a substance and the biological response it elicits.

surprising, given that the additive effects of the two ingredients together would have expected to be only "66 μM (38 μM for netupitant + 28 μM for palonosetron)." (Ex. 1005 at 343, ¶¶ 22-23.) In other words, these synergistic effects of the innovative combination are far greater than the additive effects of netupitant and palonosetron when administered separately.

58. The inventors also 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)." (Ex. 1002 at 5:13-17.) "Therefore, in another embodiment the invention provides a combination therapy for treating nausea and vomiting for five consecutive days in a patient in need thereof," where the combination therapy includes administering, *inter alia*, netupitant and dexamethasone. (*Id.* at 5:17-50.) This novel combination therapy is recited, for example, in claim 2 of the '357 patent. (*Id.* at claim 2 ("A method of treating chemotherapy induced nausea and vomiting (CINV) in a subject receiving chemotherapy comprising administering to a subject receiving chemotherapy a regimen of netupitant and a sub-therapeutic dose of dexamethasone.").)

VI. ANALYSIS OF CERTAIN LITERATURE REFERENCED BY DR. PEROUTKA

A. Herrstedt (Ex. 1010)

59. Herrstedt is a review article that summarizes the development of anti-emetic therapy with a "focus on the importance of two new classes of anti-emetics: the serotonin$_3$- and the neurokinin$_1$-receptor antagonists." (Ex. 1010 at 143.) Herrstedt discloses that historically, "[n]ausea and vomiting are ranked by patients as two of the worst adverse effects of cancer chemotherapy. Twenty-five years ago, nausea and vomiting were inevitable adverse effects of cancer chemotherapy, but the development of [these two] new and potent anti-emetics has led to a significant decrease in a number of patients suffering from chemotherapy-induced ***vomiting***." (Ex. 1010 at 143 (emphasis added).)

60. Herrstedt states that "[t]he first non-peptide NK1-receptor antagonist was developed in 1991, and the first clinical trial with one of these agents was published in 1997." (Ex. 1010 at 146.) Herrstedt also states that "large number of NK1-receptor antagonists have been investigated," but only aprepitant has been marketed, and only one other NK-1 receptor antagonist (*i.e.*, casopitant) was so far in Phase III clinical trials. (Ex. 1010 at 146.)

61. Herrstedt touts NK-1 receptor antagonists that have been "specifically developed for anti-emetic use" in the prevention of vomiting, explaining that "[a]prepitant increases the effect of a serotonin3-receptor antagonist plus a

corticosteroid against acute ***emesis*** induced by highly or moderately emetogenic chemotherapy and aprepitant is also active in the protection against ***delayed emesis***." (Ex. 1010 at 143, 146 (emphasis added).)

62. Herrstedt notes that although the introduction of aprepitant and its use in the newly developed triple therapy (aprepitant, a 5-HT_3 receptor antagonist, and dexamethasone) had largely solved chemotherapy-induced vomiting (emesis), triple therapy did not address the lack of control of nausea in existing CINV treatments. (Ex. 1010 at 148 ("Patients receiving anti-emetic prophylaxis according to the guidelines are usually protected from vomiting during the first 1-3 courses of chemotherapy. Nausea and loss of appetite are the main problems for the majority of patients.").) As a result, Herrstedt concluded that the majority of patients still "consider nausea as the main problem." (Ex. 1010 at 143.)

63. Herrstedt further teaches that because "patients consider nausea as the main problem," even with the existence of triple therapy, the "[d]evelopment of new anti-emetics with other mechanisms of action is awaited with interest." (Ex. 1010 at 143.) Herrstedt suggests some possible routes to solve the problem of lack of control of nausea in existing CINV treatments, including drugs such as gabapentin and olanzapine as potential investigational drugs for controlling nausea. (Ex. 1010 at 148-49.) Herrstedt states that "the most promising seems to be olanzapine with very high complete response rates of both nausea and vomiting,

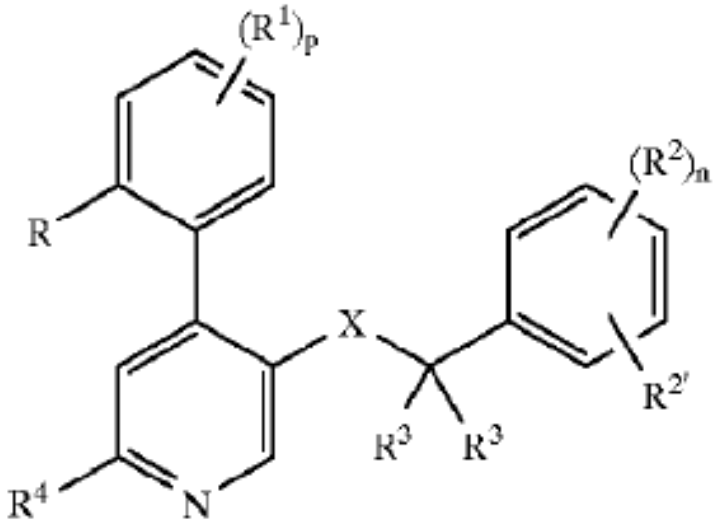
when combined with a 5-HT_3-receptor antagonist and a corticosteroid." (Ex. 1010 at 149.)

64. As another potential option, Herrstedt explains that it is "unknown if higher doses than recommended of for example corticosteroids [e.g., dexamethasone] increase the effect against nausea" because "the doses of anti-emetics are defined in studies using emesis as the primary end-point," not nausea. (Ex. 1010 at 148.)

B. Bös (Ex. 1014)

65. Bös is a U.S. Patent No. 6,297,375 that is titled "4-Phenyl-Pyridine Derivatives." (Ex. 1014 at Cover) The named inventors include, among others, Michael Bös and Torsten Hoffmann, and the patent is assigned to Hoffmann-La Roche Inc. (Ex. 1014 at Cover.) Bös issued on October, 2, 2001. (Ex. 1014 at Cover.)

66. The Bös patent describes a large class of pyridine compounds, encompassing millions of individuals compounds, only one, of which is netupitant. The invention relates to compounds for a general formula:



(Ex. 1014 at 2:01-65.) The Bös patent lists numerous options for substitutions at each of the positions in the general formula. (*Id.*) The number of iterations of substitutions totals more than a million potential compounds that could be formed.

67. The Bös patent also describes a number of uses for this class of compounds:

> Compounds of this invention are NK-1 receptor antagonists and, as such are particularly useful for treating ***depression and pain***, especially that resulting from ***inflammatory conditions*** such as migraine, rheumatoid arthritis, asthma, and inflammatory bowel disease or resulting from central nervous system (CNS) disorders such as Parkinson's disease or Alzheimer's disease. Furthermore, the

> compounds of this invention are useful as agent against ***headache***, ***anxiety***, ***multiple sclerosis***, ***attenuation or morphine withdrawal***, ***cardiovascular changes***, ***oedema***, such as oedema caused by thermal injury, ***chronic inflammatory diseases*** such as rheumatoid arthritis, ***asthma/bronchial hyperreactivity and other respiratory diseases*** including allergic rhinitis, inflammatory diseases off the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases.

(Ex. 1014 at 3:64-4:14 (emphasis added).)

68. As such, Bös roughly lists millions of NK-1 receptor antagonists and a vast number of conditions that any one of those millions of antagonists could possibly end up being useful in treating. (Ex. 1014 at 2:01-65.) Importantly, with all of these potential uses of these compounds, nausea is not included. Instead, only emesis is. (Ex. 1014 at 4:15-20 ("[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.").)

69. In addition, Bös lacks any human clinical data and only provides data from *in vivo* animal studies and *in vitro* CHO cells (cells derived from hamsters) where human NK-1 receptors were expressed. (Ex. 1014 at 18:42-19:38.) The *in vivo* animal studies were early exploratory studies on, *inter alia*, potential uses for

NK-1 receptor antagonists that used animal models for anxiety (gerbil foot tapping), motion sickness (suncus murinus), and emesis (ferrets). (Ex. 1014 at 18:42-19:38.) None of these animal models were used to assess any potential efficacy of netupitant in controlling nausea in humans. (Ex. 1014 at 14:09-30, 18:42-19:38.) Moreover, Bös makes no mention of aprepitant, nor makes any comparison of any of its disclosed compounds to aprepitant.

VII. REBUTTAL TO DR. PEROUTKA'S OPINIONS

70. For the reasons discussed below, I disagree with the opinions provided by Dr. Peroutka in his declaration in this proceeding. (*See generally* Ex. 1009.) I identify and discuss those opinions below and provide my response to them.[10]

71. For example, Dr. Peroutka opines that a POSA would have been motivated to combine teachings of certain references, with a reasonable

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[10] I have been informed and understand that claim terms are typically given their ordinary and customary meanings, as would have been understood by a POSA at the time of the alleged invention. In considering the meaning of the claims, however, I understand that one must consider the language of the claims, the specification, and the prosecution history of record. I have applied such understanding in forming my opinions here.

expectation of success, to achieve the invention of each claim as a whole. (*See, e.g.,* Ex. 1009 at ¶¶ 843, 1003, 1090, 1108, 1124, 1140, 1156, 1313.) As I explain below in Section VII.A-VII.C, I disagree with his opinion because it lacks consideration of several relevant factors and is unsupported by the references he cites. Among other shortcomings, his analysis fails to take into account the problem facing a POSA, the many different potential paths that a POSA would have considered to possibly address the problem facing the POSA, and whether any of these paths would have led to the claimed netupitant-based regimen for treating CINV.

72. As I explain below in Section VII.D, I also disagree with Dr. Peroutka's opinion regarding the unexpected synergistic effect from combining palonosetron and netupitant in a CINV treatment. For example, Dr. Peroutka opines that this combination offers "no unexpected difference when compared to aprepitant and palonosetron" because "the combination of palonosetron with *any* NK_1 receptor antagonist had a beneficial effect on nausea." (*See, e.g.*, Ex. 1009 at ¶¶ 1380, 1382 (emphasis in original).) But Dr. Peroutka does not question the data that was provided in Table 2 of Helsinn's Rule 132 declaration, which clearly shows the unexpected impact of the palonosetron-netupitant combination on substance P response. (*See* Section VII.D.) Moreover, as I explain in various places throughout this declaration, the collective data as of November 2009 clearly

showed that an aprepitant-based regimen (including a regimen combining aprepitant with palonosetron) for treating CINV failed to show a statistically significant effect on nausea. This data on aprepitant is in stark contrast to the netupitant-based regimen for treating CINV described and claimed in the '357 patent.

73. Finally, in Section VII.E, I offer my rebuttal to Dr. Peroutka's opinion that Helsinn mischaracterized data during prosecution of the '826 patent. I understand that the Rule 132 Declaration was not submitted during prosecution of the '357 patent, however, to the extent it is applicable, I explain how Helsinn's Rule 132 declaration accurately characterized the data cited in that declaration. I also explain how the cited documents, as well as other industry publications, confirm Helsinn's statements in its Rule 132 declaration, namely that aprepitant failed to show a statistically significant effect on nausea.

A. Dr. Peroutka's Analysis Fails to Consider Several Factors That Would Have Been Pertinent to a POSA

74. Dr. Peroutka opines that a POSA in November 2009 would have been motivated to replace aprepitant in triple therapy with netupitant and would have reasonably expected to succeed in doing so. (*See, e.g.,* Ex. 1009 at ¶¶ 845, 996-1002, 1087-89, 1102-07, 1118-23, 1134-39, 1151-55, 1305-12, 1324-28.) His analysis assumes that a POSA would have started with triple therapy (*e.g.*,

Herrstedt), found references disclosing netupitant (*e.g.,* Bös), and then altered triple therapy to include netupitant. As I describe below, Dr. Peroutka uses Helsinn's invention as a roadmap and fails to consider the path a POSA, who is presumed to not to have access to Helsinn's patent, would have taken.

1. Dr. Peroutka Fails to Consider the Problem Facing a POSA

75. Dr. Peroutka's analysis includes no consideration of the problem facing a POSA. In my opinion, scientific research begins with identifying an objective or goal. In the medical field, that objective or goal is often solving a problem with current treatments. In my experience, like any scientist, a POSA would have first identified a problem that they wanted to solve and then focused their research on finding a potential solution to that problem. Without any understanding of the problem facing a POSA, one cannot analyze what paths the POSA would have taken to solve the problem. And if one cannot analyze what paths a POSA would have taken, then one cannot conclude that a POSA would have a motivation to combine the references in a manner Dr. Peroutka did. Below, I provide the analysis that is missing from Dr. Peroutka's declaration.

76. As I explained in the background section, *supra* Section V.A., a POSA would have known that chemotherapy-induced nausea and chemotherapy-induced vomiting are two separate adverse events associated with chemotherapy and often need to be treated individually. (Ex. 2036 at 517, 528.) For example, CINV

clinical trials used various primary and secondary endpoints that independently measure the occurrence of each side effect. I have summarized some of the endpoints that we used in the following chart:

Side Effect of Chemotherapy	Corresponding Endpoint
Acute chemotherapy-induced vomiting	No emesis (0-24 hours)
Delayed chemotherapy-induced vomiting	No emesis (24-120 hours)
Overall chemotherapy-induced vomiting	No emesis (0-120 hours)
Acute chemotherapy-induced nausea	No nausea (0-24 hours)
Delayed chemotherapy-induced nausea	No nausea (24-120 hours)
Overall chemotherapy-induced nausea	No nausea (0-120 hours)
Breakthrough emesis	No rescue antiemetics

(*See, e.g.*, Ex. 2037 at 585.)

77. A POSA would have understood that during the relevant time frame (as I defined above in Section IV), there were available CINV treatments that effectively controlled emesis. For example, the use of aprepitant was one of the three compounds in triple therapy (aprepitant, 5-HT_3 receptor antagonist, dexamethasone) improved the control of acute and delayed emesis as compared to standard therapy (5-HT_3 receptor antagonist and dexamethasone). (Ex. 2036 at 521.) Both clinicians and patients agreed, however, that chemotherapy-induced nausea remained a problem for patients undergoing cancer treatment. (*See, e.g.*, Ex. 2036 at 528 ("The control of nausea in patients receiving moderately and

highly emetogenic chemotherapy remains a significant problem."); Ex. 2001 at 1874 ("The control of nausea in patients receiving MEC or HEC remains a significant problem."); Ex. 1010 at 143 ("Today, the majority of patients consider nausea as the main problem."); Ex. 1010 at 148 ("Nausea and loss of appetite are the main problems for the majority of patients."); Ex. 2037 at 573 ("patients often experience more nausea than vomiting").)

78. Available clinical trial data for triple therapy indicated that triple therapy was not effective in controlling nausea. For example, two large Phase III trials of aprepitant plus a 5-HT_3 receptor antagonist and dexamethasone for the prevention of CINV in patients receiving HEC demonstrated no statistically significant improvement in nausea. In these studies, "no nausea" was reported in 48% of the patients who received aprepitant and in 44% of the patients in the control group. (*See* Ex. 1037 at 4116.)

79. In a similar study of breast cancer patients who were receiving HEC, aprepitant was added to ondansetron and dexamethasone for the prevention of CINV to assess whether aprepitant was effective in treating nausea. No statistically significant improvement in nausea was observed, and in fact, the same percentage of patients (33%) in both the control group and the group receiving aprepitant reported "no nausea." (Ex. 1034 at 2827-29.) Similarly, there were no significant differences between the two treatment groups in reports of significant

nausea with 61% of the aprepitant patients reporting "no significant nausea" versus 56% of the control patients. (Ex. 1034 at 2827.)

80. Three Phase III studies in patients with solid tumors receiving a single cycle of HEC and a regimen containing aprepitant plus dexamethasone plus ondansetron demonstrated that "[t]here was no between-group difference in the number of patients with no significant nausea in any of the three studies." (Ex. 2001 at 1861-62.) Another large phase III trial in patients with breast cancer treated with MEC, an aprepitant regimen, compared with a control regimen, demonstrated "no significant difference between the groups during the overall phase for the percentage of patients reporting no nausea or no significant nausea." (Ex. 2001 at 1864.)

81. As a result, at the relevant time, a POSA would have known that "[t]he control of nausea was not improved with the use of aprepitant." (*See, e.g.*, Ex. 2036 at 522; *see also id.* at 527 ("Aprepitant did not improve nausea in the study."); *id.* at 529 ("[A]prepitant . . . has not been effective in controlling nausea."); Ex. 1034 at 2828-29 ("There was no significant effect of aprepitant on nausea . . . ."); Ex. 1048 at 531-34 ("[T]he present study has revealed that use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, while there was no difference in the nausea domain."); Ex. 2037 at 587 ("A randomized phase III study (866 patients) showed

that an aprepitant regimen (aprepitant, ondansetron, and dexamethasone) is better than a standard regimen (ondansetron and dexamethasone) for preventing vomiting . . . however, 40% of patients (undergoing either regimen) still experienced significant nausea.") (citing Ex. 1034 (showing that the aprepitant regimen did not have a statistically significant effect on nausea compared to the control regimen of standard therapy).) In fact, the Emend® (aprepitant) label expressly states that aprepitant does not provide any statistically significant improvement on nausea. (*See* Section VII.E.1; *see also* Ex. 1016 at 2086 ("According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea . . . .").)

82. As a result, a POSA researching the treatments for CINV would have understood that the problem they faced was the need for an improved treatment for CINV that allowed control of chemotherapy-induced nausea.

2. Dr. Peroutka Fails To Analyze the Various Paths a POSA Could Have Taken in an Attempt to Solve the Problem They Faced

83. As I explained above, a POSA researching the potential treatments for CINV would have understood that the problem they faced was the need for an improved treatment for CINV that allowed control of chemotherapy-induced nausea. Dr. Peroutka, however, provides no analysis of the various paths a POSA could have (and likely would have) considered in attempting to solve this problem.

84. Understanding that triple therapy was effective against emesis, one path that a POSA would have considered worth investigating is adding a fourth drug that may be useful in the control of chemotherapy-induced nausea to triple therapy. (Ex. 2036 at 516 ("Future studies may consider the use of palonosetron, aprepitant and casopitant with other antiemetic agents (e.g. olanzapine, gabapentin, cannabinoids) in moderately and highly emetogenic chemotherapy . . . .").) In considering this potential path, a POSA would not have selected an agent with the same mechanism of action as aprepitant because "[t]he prevention of nausea and vomiting involves a complex interaction between multiple organs and multiple neurotransmitters," and therefore, "the most effective antiemetic regimen . . . is likely to involve a combination of various antiemetic agents with different mechanisms of action." (Ex. 2001 at 1875; Ex. 2036 at 526 ("It is very unlikely that established nausea and vomiting will respond to an agent in the same drug class after unsuccessful prophylaxis with an agent with the same mechanism of action.").) As explained by the NCCN Clinical Practice Guidelines in Oncology from 2009, "each antiemetic agent predominantly blocks one receptor type. . . . Therefore, no single agent can be expected to provide complete protection from the various emetic phases of chemotherapy." (Ex. 2037 at 573.) Accordingly, "[t]he general principle of breakthrough treatment is to give an additional agent as needed from a different drug class." (Ex. 2037 at 590.)

85. As I explained above in Section V.C., promising antinausea agents with different mechanisms of action than aprepitant (such as olanzapine, gabapentin, dronabinol, and/or nabilone) had been identified by November 2009, and a POSA would have considered adding them to the triple therapy regimen. (*See, e.g.*, Ex. 1010 at 149.) For example, publications at that time had reported that the "most promising" antiemetic at the time was "olanzapine with very high complete response rates of both nausea and vomiting, when combined with a 5-HT_3-receptor antagonist and a corticosteroid" (Ex. 1010 at 149.)

86. In fact, my research post-2009 later confirmed that olanzapine added to triple therapy "significantly improved nausea prevention, as well as the complete-response rate" in patients receiving highly emetogenic chemotherapy. (Ex. 2039 at 134.) In a Phase III trial conducted in 2016, we compared the combination of olanzapine plus triple therapy (*i.e.*, olanzapine plus dexamethasone, aprepitant or fosaprepitant, and a 5-HT_3–receptor antagonist) to triple therapy alone and found that "[t]he proportion of patients with no chemotherapy-induced nausea was significantly greater with olanzapine . . . ." (Ex. 2039 at 134.) In the first 24 hours after chemotherapy, 74% of patients who received olanzapine plus triple therapy were reported to have experienced "no nausea," compared to 45% of patients who received triple therapy. (Ex. 2039 at 134.) From 25 to 120 hours after chemotherapy, 42% of patients who received olanzapine plus triple therapy

were reported to have experienced "no nausea," compared to 25% of patients who received triple therapy. (Ex. 2039 at 134.) And for the overall 120-hour period, 37% of patients who received olanzapine plus triple therapy were reported to have experienced "no nausea," compared to 22% of patients who received triple therapy. (Ex. 2039 at 134.)

87. As a further example, by 2009, a clinical study had been conducted in a small number of patients receiving adjuvant chemotherapy (doxorubicin and cyclophosphamide) for breast cancer. (Ex. 2036 at 525.) The study results "suggested that the anti-epileptic gabapentin may reduce delayed nausea." (Ex. 2036 at 525.) Because this study was conducted in a small number of patients, the authors suggested that "[f]urther studies [would] be necessary to determine the efficacy of this agent." (Ex. 2036 at 525.) A POSA, moreover, would have known about the potential anti-nausea effects of gabapentin and considered it as a "potential new anti-emetic[]." (Ex. 1010 at 149; Ex. 2036 at 525.) But in his declaration, Dr. Peroutka failed to consider whether a POSA would have been motivated to add gabapentin to the triple therapy regimen.

88. Lastly, by 2009, in "a systematic review of the efficacy of oral cannabinoids in the prevention of nausea and vomiting, it was found that cannabinoids were slightly better than conventional antiemetics (e.g., metoclopramide, phenothiazines, haloperidol)." (Ex. 1019 at 1147.) The NCCN

guidelines had likewise suggested the use of cannabinoids for breakthrough treatment and recent evidence had indicated that CB_2 receptors may have a role in controlling emesis and/or nausea. (Ex. 2036 at 525; Ex. 2037 at 578, 590 (listing dronabinol and nabilone).)

89. In fact, by November 2009, two oral formulations of cannabinoids (dronabinol and nabilone) had been approved by the FDA for use in CINV. (Ex. 2036 at 525.) Dronabinol was indicated for "nausea and vomiting associated with chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments." (Ex. 2042 at 7.) Importantly, the clinical trials that were included in the FDA-approved labeling for dronabinol reported that "decreases in nausea" were seen. (Ex. 2042 at 5.) Nabilone was indicated for "the treatment of the nausea and vomiting associated with cancer chemotherapy in patients who have failed to respond adequately to conventional antiemetic treatments." (Ex. 2043 at 5.) The clinical trials that were included in the FDA-approved labeling for nabilone also evaluated nabilone for its "effectiveness and safety in the treatment of nausea and vomiting induced by cancer chemotherapy . . . ." (Ex. 2043 (Nabilone label) at 5.) Accordingly, in 2009, a POSA would have thought that cannabinoids were a potentially useful option in the control of chemotherapy-induced nausea based on their mechanism of action. (Ex. 2036 at 528; Ex. 2001 at 1874 ("Given their differing mechanism of action,

cannabinoids may be useful in chemotherapy-induced nausea; however, trials that investigate the combination of a cannabinoid and aprepitant in the prevention of CINV have yet to be conducted.”).)

B. Dr. Peroutka Fails to Show a POSA Would Have Been Motivated to Select Netupitant for Triple Therapy

90. As I explained above in Section VII.A, Dr. Peroutka failed to consider the problem facing a POSA and the various paths that a POSA would have considered to try and solve the problem. Instead of performing this analysis, Dr. Peroutka assumes that a POSA would straightaway look to replace aprepitant in the triple therapy with another NK-1 receptor antagonist (netupitant). (*See, e.g.,* Ex. 1009 at ¶¶ 845, 996-1002, 1087-89, 1102-07, 1118-20, 1134-36, 1151-55, 1305-12, 1324-28.) But even if I were to assume (for the sake of argument) that a POSA would to start with a three-drug regimen and seek to replace aprepitant with another NK-1 receptor antagonist, Dr. Peroutka failed to provide any explanation of why a POSA would select netupitant from the many other NK-1 receptor antagonists that were available in November 2009.

91. As discussed above in Section V.B.3, a very large number of NK-1 receptor antagonists were being investigated by November 2009. At that time, only aprepitant has been FDA-approved and marketed, and only one other NK-1 receptor antagonist (casopitant) had progressed as far as Phase III clinical trials.

(Ex. 1010 at 146.) A POSA who was focused on using a different NK-1 receptor antagonist than aprepitant would have been aware of the "remarkable number of small molecule NK1 receptor antagonists [that] were identified by many pharmaceutical companies in the last decade." (Ex. 1011 at 1362.) In my opinion, the POSA would then have weighed the publicly disclosed benefits and drawbacks of each NK-1 receptor antagonist and narrowed the field down to the most promising candidates. The POSA would have considered any relevant data from these promising candidates, and especially any comparative data with aprepitant. But Dr. Peroutka's declaration fails to include any such analysis.

92. Dr. Peroutka opines that a POSA would have had reason to substitute netupitant for aprepitant in triple therapy because netupitant was "shown to be a 'potent and selective antagonist" (*see, e.g.*, Ex. 1009 at ¶ 861) and "excellent CNS penetration." (*see, e.g., id.* at ¶¶ 853, 883). Dr. Peroutka further opines that a POSA would conclude that netupitant would be an "favorable alternative NK1 receptor antagonist to aprepitant" (*See, e.g.*, *id*. at ¶¶ 884, 1000) According to Dr. Peroutka, a POSA would have "expected continued efficacy" based on his proposed substitution. (*See, e.g.*, *id.* at ¶¶ 836, 997.) I disagree with Dr. Peroutka's opinion for several reasons.

93. Dr. Peroutka does not identify any shortcoming in triple therapy that a POSA would have thought would have been obviated by replacing aprepitant with

netupitant. While Dr. Peroutka opines that his proposed replacement would have achieved "continued efficacy," he offers no evidence in support of this opinion, and in particular, he points to no studies that compared netupitant and aprepitant. (*See, e.g.*, *id.* at ¶¶ 836, 997.) Importantly, and in my opinion, just because both aprepitant and netupitant are both part of the same drug class of NK-1 receptor antagonists does not mean their expected efficacy would have been the same, including across different indications. Any POSA would have known that drugs in the same drug class could not simply be mixed-and-matched for any indication, as ultimately shown by Helsinn's comparative analysis between netupitant and aprepitant. (*See* Section VII.E.)

94. By way of background, CNS penetration is a property common to many NK-1 receptor antagonists. CNS penetration is also associated with treating a wide variety of different disorders other than emesis, including depression, anxiety, Parkinson's disease, and Alzheimer's disease. (Ex. 1014 at 3:64-4:14.) Dr. Peroutka fails to provide any reason that a POSA evaluating the CNS penetration data in Bös would find netupitant to be superior in any way to aprepitant for treating CINV, let alone in treating nausea. Moreover, Bös does not contain any data comparing the CNS penetration of netupitant to other NK-1 receptor antagonists, so a POSA could not predict or conclude based on these

publications whether netupitant would have been an excellent alternative to aprepitant, even for the discrete metric of CNS penetration.

95. In fact, the publicly available data from a clinical trial to evaluate the effects of aprepitant in treating nausea in CINV in the manufacturer's label found that aprepitant did not have a statistically significant impact on nausea. Moreover, there was no clinical data available from any studies in humans that evaluated the potential efficacy of netupitant in the treatment of nausea or any other condition. Dr. Peroutka does not address the lack of available clinical data for netupitant at all in his declaration.

96. Similarly, Dr. Peroutka cites Bös to opine that "netupitant was shown to potently and selectively inhibit the NK_1 receptor, and likewise antagonized NK1 receptor-induced foot tapping after oral administration , which was indicative of successful NK_1 receptor antagonism." (*See, e.g.*, Ex. 1009 at ¶ 997 (citing Ex. 1014 (Bös) at 14:32-19:37).) Bös lacks any human clinical data and instead only provides data from *in vivo* studies in animals. (*Id.*) Dr. Peroutka provides no explanation of how foot tapping in animal would lead a POSA to conclude that netupitant could be effective in treating CINV at all in humans, let alone the nausea component of CINV. Moreover, Bös does not mention of aprepitant at all, nor does Bös compare any of its disclosed compounds to aprepitant. Likewise, and contrary to Dr. Peroutka's opinion, Bös does not include any express language (let

alone data) to suggest that netupitant was a "favorable alternative NK_1 receptor antagonist to aprepitant." (*See, e.g.*, Ex. 1009 at ¶¶ 884, 1000) In my opinion, a POSA would not conclude that the clinical efficacy of two different compounds is comparable without sufficient data to support that conclusion.

97. In my opinion, the CNS penetration and oral antagonistic activity for netupitant that was cited by Dr. Peroutka for his opinions would not have motivated a POSA to make any modifications to the three existing components of the gold-standard triple therapy, including swapping out aprepitant for another member of the same NK-1 receptor antagonist class given that aprepitant had shown excellent efficacy against emesis. (Ex. 1048 at 532 ("The NK-1 antagonist aprepitant is a potent new anti-emetic which has demonstrated clear superiority over existing anti-emetic modalities.")."); *see also id.* at 534 ("[T]he present study has revealed that use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting . . . .").)

C. Dr. Peroutka Fails to Demonstrate that a POSA Would Have Reasonably Expected that Substituting Netupitant for Aprepitant in Triple Therapy Would Have Treated Both Nausea and Vomiting

98. Dr. Peroutka opines that a POSA "would have had a reasonable expectation that the substitution of a second generation NK_1 receptor antagonist (netupitant) for a first generation NK1 receptor antagonist (aprepitant) would work

in the same manner to achieve similar (or improved) outcome." (*See, e.g.*, Ex. 1009 at ¶ 1000.) I disagree with Dr. Peroutka's opinion.

99. By way of background, I understand that each independent claim of the '357 patent requires that the claimed method treat ***both nausea*** and vomiting. (Ex. 1002 at claim 1 ("A method of treating chemotherapy induced ***nausea*** and vomiting . . . .), claim 2 (same), claim 4 ("A method of treating chemotherapy induced ***nausea*** and vomiting (CINV) comprising inducing . . . blood levels of palonosetron and netupitant effective to treat said CINV.").)

100. Dr. Peroutka has not provided any evidence that shows that a POSA could reasonably expect that a netupitant-based regimen that resulted from replacing aprepitant with netupitant in the gold-standard triple therapy would have treated both nausea and vomiting. (*See, e.g.,* Ex. 1009 at ¶¶ 999-1002.) None of his cited references (Bös and Hoffmann) discuss netupitant's effect on nausea.

D. Dr. Peroutka Fails to Rebut Unexpected Synergistic Effects of Combining Netupitant and Palonosetron

101. Dr. Peroutka further opines that the combination of netupitant and palonosetron had no unexpected synergy. (Ex. 1009 at ¶¶ 1380-86.) For example, he states that "a POSA would have understood" the data in Table 2 of Rule 132 declaration submitted by Helsinn "to show the combination of palonosetron with

any NK_1 receptor antagonist had a beneficial effect on nausea." (*Id.* at ¶¶ 1380, 1382 (emphasis in original).) I disagree with Dr. Peroutka's opinion.

102. As an initial matter, Dr. Peroutka does not challenge the underlying data that demonstrates the synergistic effect of the palonosetron-netupitant combination on substance P response. (*See* Section V.D, discussing the Rule 132 declaration data on substance P response.)

103. As I discuss further below in Section VII.E, the collective data available to a POSA at the relevant time for aprepitant did not show any statistical significance over the control in its prevention of nausea. This finding is consistent with the clinical studies, including in the labeling for Emend® (aprepitant) and other disclosures in the prior art as of November 2009. In contrast, and as I discussed in detail earlier in his declaration, Section V.D, Helsinn's data showed that the combination of netupitant and palonosetron had a statistically significant effect on nausea. (*See* Section VII.E.2.)

E. Helsinn Did Not Mischaracterize Any Data During Examination

1. The Emend® Label and Other Art Show that Aprepitant Did Not Achieve a Statistically Significant Reduction Against Nausea

104. Dr. Peroutka opines that "contrary to Helsinn's representations to the USPTO, experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea." (Ex. 1009 at ¶¶ 1330-34.) Dr. Peroutka also

opines that, based on Campos (Ex. 1023), "[a]prepitant was known to provide anti-nausea therapeutic effect during the acute period following administration of highly emetogenic chemotherapy."

105. I disagree with Dr. Peroutka. As an initial matter, Campos is a reference that was published in 2001 by scientists at Merck and prior Merck's studies in the FDA-approved Emend® (aprepitant) label. (Ex. 1009 at ¶¶ 1352-54.) And as I explain below, the Emend® label shows that aprepitant did not achieve a statistically significant reduction in either nausea or significant nausea. This fact is confirmed by other industry publications, including ones cited by Dr. Peroutka.

106. By way of background, Emend® is the brand name for oral aprepitant tablets that are sold by Merck. (Ex. 2002.) The FDA approved the New Drug Application filed for aprepitant in 2003. (Ex. 2002.)

107. During prosecution of the '826 patent, the following two tables (Table 1 and Table 2) copied directly from the text of the Emend® label were cited in the Rule 132 Declaration.[11] These two tables clearly show that aprepitant's

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[11] In his declaration, Dr. Peroutka cites the Emend® label from 2008. (*See, e.g.*, Ex. 1009 at, ¶ 1334 (citing Ex. 1030).) But during examination, Helsinn

effect on nausea and significant nausea is ***not*** statistically significant for patients receiving HEC, as compared to standard therapy and indicated by "NS**" provided for the p-Value:

Table 1

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 1 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 260)† %	Standard Therapy (N = 261)† %	p-Value
* * * *			
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.

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referenced the Emend® label from 2003 (*see, e.g.,* Ex. 1005 at 346 (TABLE 2 referring to Ref. E), 350 (describing Ref. E as the March 27, 2003 Emend® label)), which I understand is Exhibit 2016 in this proceeding. For purposes of my declaration, I reference Exhibit 1030 cited by Dr. Peroutka, but my opinions remain the same for Exhibit 2016 because the underlying data is the same.

Table 2

Percent of Patients Receiving Highly Emetogenic Chemotherapy Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 261)† %	Standard Therapy (N = 263)† %	p-Value
* * * *			
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.
‖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.

(*Compare* Ex. 1005 at 330, *with* Ex. 1030 at 4-5 (annotations added).)

108. Similarly, the following table copied directly from the text of the Emend® label clearly shows that aprepitant's effect on nausea and significant nausea is ***not*** statistically significant for patients receiving MEC, as compared to standard therapy and indicated by "NS" provided for the p-Value:

Table 3

Percent of Patients Receiving Moderately Emetogenic Chemotherapy Responding by Treatment Group and Phase — Cycle 1

ENDPOINTS	Aprepitant Regimen (N = 433)† %	Standard Therapy (N = 424)† %	p-Value
PRIMARY ENDPOINT			
Complete Response‡	51	42	0.015
OTHER PRESPECIFIED ENDPOINTS			
No Emesis	76	59	NS*
No Nausea	33	33	NS
No Significant Nausea	61	56	NS
No Rescue Therapy	59	56	NS
Complete Protection	43	37	NS

†N: Number of patients included in the primary analysis of complete response.

(*Compare* Ex. 1005 at 330, *with* Ex. 1030 at 7-8 (annotations added).)

109. In my declaration, I have cited many prior art references and clinical studies that expressly state that aprepitant does not improve the control of nausea. (*See* Section VI.A.) (*See, e.g.*, Ex. 2036 at 522, 527 ("Aprepitant did not improve nausea in the study."); *id.* at 529 ("[A]prepitant . . . has not been effective in controlling nausea."); Ex. 1034 at 2828-29 ("There was no significant effect of aprepitant on nausea . . . ."); Ex. 1048 at 531-34 ("[T]he present study has revealed that use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, while there was no difference in the nausea domain."); Ex. 2037 at 587 ("A randomized phase III study (866 patients) showed that an aprepitant regimen (aprepitant, ondansetron, and dexamethasone) is

better than a standard regimen (ondansetron and dexamethasone) for preventing vomiting . . . however, 40% of patients (undergoing either regimen) still experienced significant nausea.”).) My opinion is confirmed by many of the references that Dr. Peroutka cites for his opinions. For example, Herrington (Ex. 1016), a reference relied upon by Dr. Peroutka, cites to the Emend® label and states that “[a]ccording to its package insert, ***aprepitant fails to demonstrate*** improved efficacy over placebo for the prevention of nausea . . . .” (Ex. 1016 at 2086.) Yeo (Ex. 1048), also a reference relied upon by Dr. Peroutka, similarly provides that aprepitant makes “no difference in the nausea domain” and that “nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy.” (Ex. 1048 at 6.)

110. All these references post-date Campos, a publication from 2001 about a pre-approval study conducted by scientists at Merck on aprepitant and that is cited by Dr. Peroutka. (*See* 1009 at ¶¶ 1352-53.) In my opinion, a POSA would be skeptical about the study results reported in Campos (Ex. 1023), and at the very least, would not be consider this study to be informative in view of more recent studies, including the Emend® clinical trial studies, that reported that the aprepitant treatment failed to demonstrate improved efficacy over placebo for the prevention of nausea. In my opinion, Campos is an outlier, due to at least the fact that it reports median visual analog scale (VAS) nausea scores of 7 mm or less on Days 1

to 5 for every treatment group tested (Treatment Groups 1-IV). (Ex. 1023 at 1764, Table 4.) In other words, Campos reported that 100% of its patients, regardless of treatment regimen, experienced no significant nausea (*i.e.*, nausea VAS of <25 mm) for the overall time period of Days 1 to 5, which is not consistent with what a POSA would have interpreted as a reliable result for patients receiving cisplatin, which was well-known to be HEC. (Ex. 1023 at 1764, Table 4.)

111. Dr. Peroutka opines that the data in the Emend® label "shows reduction of nausea (and in particular reducing significant nausea) for patients" because "while statistical significance was not calculated for nausea parameters, the 'complete protection' value includes a lack of significant nausea in its metric." (Ex. 1009 at ¶ 1334.) Dr. Peroutka further opines that "a POSA would have understood this ['complete protection' endpoint] data to illustrate an improvement in the patients receiving aprepitant, including a decrease of significant nausea." (Ex. 1009 at ¶ 1336.)

112. I disagree with the interpretation of the data in the Emend® label that Dr. Peroutka offers for his opinions. For context, the Emend® label states that "complete protection" requires (1) no emetic episodes; (2) no rescue therapy; and (3) no significant nausea. (Ex. 1030 at 4.) A POSA reading the Emend® label would understand that the data in the Emend® label does not show a statistically significant reduction of nausea or significant nausea for at least two reasons.

113. **First**, statistical significance was calculated for the distinct nausea endpoints, and the results for "no nausea" and "no significant nausea" were found to be "not statistically significant" between the aprepitant regimen and the standard therapy. (Ex. 1030 at 4-5, 7-8.) The fact that the nausea results were found "not statistically significant" between these two groups means that there is no evidence of a difference between them in the control of nausea. (*See, e.g.*, Ex. 1016 at 2086 (explaining that it is "unlikely that there is a true difference present").) In other words, there is insufficient evidence to conclude that aprepitant made a real difference in whether the patients experienced "no nausea" or "no significant nausea."

114. **Second**, a POSA would not understand a difference in "complete protection" between aprepitant and standard therapy to be the same as a statistically significant difference in "no significant nausea." (*See* Ex. 1030 at 4-5, 7-8.) The "complete protection" value is a "composite" endpoint. (*See* Ex. 1048 at 531; Ex. 2001 at 1860, Table IV; Ex. 1022 at 1442.) Here, that composite endpoint combines data from three separately measured endpoints: (1) "no emesis," (2) "no use of rescue antiemetics," and (3) "no significant nausea." Dr. Peroutka opines that "a POSA would have understood this ['complete protection' endpoint] data to illustrate an improvement in the patients receiving aprepitant, including a decrease of significant nausea." (Ex. 1009 at ¶ 1336.) I disagree. A POSA would not

understand a difference in "complete protection" between aprepitant and standard therapy, to be the same as a statistically significant difference in "no significant nausea." (*See* Ex. 1030 at 4-5, 7-8.) Moreover, a POSA reading the Emend® label would not ignore the label's express data on "no significant nausea" itself to instead focus on a composite endpoint when the POSA was specifically evaluating a drug for potential control of nausea. As I have discussed above, the data in the Emend® label that assessed nausea as an individual endpoint found no statistical significance between the aprepitant regimen and standard therapy. Furthermore, both the "no emesis" and "no use of rescue antiemetics" endpoints, which are used to measure the ability of aprepitant to control vomiting only and exclude nausea (*see* Ex. 2036 at 521-22), were found to be statistically significant. (*See* Ex. 1030 at 4-5, 7-8.) This data thus suggests that the significant difference in "complete protection" was actually due to significant improvements in the "no emesis" and/or "no use of rescue antiemetics" components of the "complete protection" endpoint. (*See* Ex. 1030 at 4-5, 7-8.)

2. Combination of Palonosetron and Netupitant Provided a Statistically Significant Effect on Nausea, When Other Combinations Did Not

115. Dr. Peroutka opines that a POSA would have understood that the data sets provided in Table 6 (*i.e.*, Example 5) of the specification and Table 2 of the Rule 132 Declaration submitted during prosecution of the '826 patent "illustrate[]

that aprepitant has an effect on nausea comparable to netupitant." (Ex. 1009 at ¶¶ 1341-51.) I disagree. Once again, Dr. Peroutka ignores the importance of statistical significance and does not identify any data that shows aprepitant had a statistically significant impact on the control of nausea. As I explain in detail below, the combination of palonosetron and netupitant did what aprepitant in combination with other drugs (with or without palonosetron) failed to do, which is demonstrate a statistically significant improvement in nausea.

116. In Table 6 of the '826 patent specification, which I have included below, the "Palo + Netu 300 mg" combination provided a statistically significant improvement in delayed "no nausea" as compared to palonosetron alone, as shown by the green highlight. The "Palo + Netu 300 mg" combination also provided a statistically significant improvement in "no significant nausea" and delayed "no nausea" as compared to palonosetron alone in the overall, acute, and delayed context, as also shown by the green highlight:

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 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

*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

(Ex. 1001 at Table 6.) In contrast, the "Aprepitant Regimen" and "Palo + Aprep 285 mg" did not report any statistical significant improvement in either "no nausea" or "no significant nausea," as compared to the palonosetron alone.

117. As another example, in Table 2 of the Rule 132 Declaration, which I have included below and was submitted during prosecution,[12] the "Palo + Netu

[12] The "Palo + Netu 300 mg" combination in Table 6 of the '826 patent specification corresponds to the "Palo + Netu (HEC)" combination Column 1 of

(HEC)" combination provided a statistically significant improvement in delayed "no nausea" as compared to palonosetron alone, as shown by the green highlights. The "Palo + Netu (HEC)" combination also provided a statistically significant improvement in "no significant nausea" and delayed "no nausea" as compared to palonosetron alone in the overall, acute, and delayed context, as also shown by the green highlight:

Table 2 in the Rule 132 Declaration. The "Aprepitant Regimen" combination in Table 6 of the '826 patent specification corresponds to the "Ondan + Aprep (HEC)" combination Column 2 of Table 2 in the Rule 132 Declaration. The "Palo + Aprep 285 mg" combination in Table 6 of the '826 patent specification corresponds to the "Palo + Aprep (MEC)" combination Column 6 of Table 2 in the Rule 132 Declaration.

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
[a] Helsinn Study NETU-07-07
[b] Helsinn Study NETU-08-18
[c] Warr *et al.* (2005) (Ref. D)
[c1] FDA-Approved Prescribing Information for Emend® (aprepitant) (results of two studies reported) (Ref. E)
[d] Herrington *et al.* (2008) (Ref. F)
[e] Grunberg *et al.* (2008) (Ref. G)
[f] Yeo *et al.* (2009) (Ref. H)
[g] Longo *et al.* (2012) (Ref. I)

(Ex. 1005 at 346 (file history of '462 application).)

118. In contrast, the "Ondan + Aprep (HEC)" (Column 2) and "Palo + Aprep (MEC)" (Column 6) did not report any statistical significant improvement in either "no nausea" or "no significant nausea," as compared to the palonosetron alone. The orange highlight, however, shows that those data points were non-comparative studies where statistical significance was not evaluated. As a result, a POSA would not have been able to draw any conclusions from their data in relation to aprepitant's effect on nausea because its difference from the control has not been evaluated.

119. The combination of aprepitant and palonosetron in Column 5, however, did not result in a statistically significant reduction in nausea or significant nausea in the HEC. The data from Column 5 was obtained from a publication by Herrington in (Ex. 1016) and cited below the table as Reference "d."

120. In the clinical study described in the Herrington publication, all three patient arms (A, B, and C) received 0.25 mg of palonosetron intravenously on Day 1 and dexamethasone on Days 1-4. (Ex. 1016 at 2080.) The patients in Arm A also received aprepitant on Days 1-3. The patients in Arm B received aprepitant on Day 1 and placebo on Days 2-3. The patients in Arm C received placebos on Days 1-3 and no aprepitant at all. (Ex. 1016 at 2080.) But no matter whether or how much aprepitant was administered to a given arm, the "incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms." (Ex. 1016 at 2084.) Herrington stated that, because there were no statistically significant differences in nausea between the three patient arms, it is "unlikely that there is a true difference present because previously published data has not found a disparity." (Ex. 1016 at 2086.) Accordingly, Herrington concluded that aprepitant, even when combined with palonosetron, "fails to demonstrate improved efficacy over placebo for the prevention of nausea (overall and significant nausea) in acute or delayed phases." (Ex. 1016 at 2086.)

121. Dr. Peroutka opines that the 132 Declaration excluded some data from Warr (Ex. 1034) in Column 4, and some of the data from Yeo (Ex. 1048) in column 7. (Ex. 1009 at ¶¶ 1367-70.) I note that the 132 Declaration cited these publicly-available documents as "c" and "f" below:

> [a] Helsinn Study NETU-07-07
> [b] Helsinn Study NETU-08-18
> [c] Warr *et al.* (2005) (Ref. D)
> [d] FDA-Approved Prescribing Information for Emend®
> [d] Herrington *et al.* (2008) (Ref. F)
> [e] Grunberg *et al.* (2008) (Ref. G)
> [f] Yeo *et al.* (2009) (Ref. H)
> [g] Longo *et al.* (2012) (Ref. I)

(Ex. 1005 at 346 (file history of '462 application).)

122. Dr. Peroutka states that "[i]t 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." (Ex. 1009 at ¶ 1370.) I disagree. In my opinion, both of these are consistent with the statements in the Rule 132 declaration that the combination of palonosetron with the gold-standard NK-1 inhibitor (aprepitant) showed no synergistic effects. Warr states "[t]here were no significant differences between the two treatment groups in reports of overall nausea (VAS < 5 mm; 33% for both) or significant nausea (VAS < 25 mm; aprepitant 61%, control 56%)." (Ex.

1034 at 2827; *see also id.* at 2828-29 ("There was no significant effect of aprepitant on nausea").) Yeo states "the present study has revealed that use of aprepitant-based anti-emetic regimen improves patients' quality of life, especially on aspects of control of vomiting, ***while there was no difference in the nausea domain***." (Ex. 1048 at 534 (emphasis added).)

123. I disagree with Dr. Peroutka's opinions about the Emend® label (Ex. 1009 at ¶¶ 1371-73) for the same reasons I explained above in Section VII.E.1. The Emend® label shows that aprepitant did not achieve a statistically significant reduction in either nausea or significant nausea. This fact is confirmed by other industry publications, including ones cited by Dr. Peroutka.

124. Dr. Peroutka opines that "there are significant differences" between Helsinn's studies and the study used for the data Column 6 that prevent comparison. (Ex. 1009 at ¶¶ 1374-79.) By way of background, Column 6 contains data from Grunberg (Ex. 1035), a publicly-available clinical study that found aprepitant did not have a statistically significant effect on nausea. As I discussed above, Column 6 in Table 2 is the same as "Palo + Aprep 285 mg" in Table 6 of the '826 patent specification. For the same reasons as discussed for Table 6 of the '826 patent specification, the "Palo + Aprep 285 mg" regimen from Column 6 (Grunberg (Ex. 1035)) did not report any statistical significant

improvement in either "no nausea" or "no significant nausea," as compared to the palonosetron alone. (Ex. 1001 at Table 6.)

VIII. CONCLUSION

125. 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: September 3, 2025

By: _____

Rudolph M. Navari, M.D.

APPENDIX A

Exhibit No.	Description	Previously Submitted?
1009	Expert Report of Dr. Peroutka (Ex. 1009) and references cited therein	X
2001	Curran, P. et al., *Aprepitant A Review of its Use in the Prevention of Nausea and Vomiting*, Drugs 2009: 69 (13): 1853-1878	X
2002	EMEND® (aprepitant) FDA Approval Letter, NDA 21-549, dated March 26, 2003, available at https://www.accessdata.fda.gov/drugsatfda_docs/nda/2003/21-549_Emend_Approv.pdf	X
2004	Emend IV (fosaprepitant) FDA Approval Letter, NDA 22-023, dated January 25, 2008, available at https://www.accessdata.fda.gov/drugsatfda_docs/NDA /2008/022023s000_Approv.pdf	X
2016	EMEND® label, March 2003	X
2036	Navari, R.M. Pharmacological Management of Chemotherapy-Induced Nausea and Vomiting. Drugs 69, 515–533 (2009). https://doi.org/10.2165/00003495-200969050-00002 (Published March 2009)	
2037	Ettinger et al., Antiemesis Clinical Practice Guidelines in Oncology, Journal of the National Comprehensive Cancer Network, 7(5): 572-595 (May 2009)	
2039	Navari et al, "Olanzapine for the Prevention of Chemotherapy-Induced Nausea and Vomiting", New England Journal of Medicine, 375(2), 134-142, 2016, https://doi.org/10.1056/NEJMoa1515725	
2042	MARINOL® (Dronabinol) label	
2043	CESAMET™ (Nabilone) label	
2044	Navari CV	

Exhibit No.	Description	Previously Submitted?
2045	Albert, J.S. et al., "Structural analysis and optimization of NK1 receptor antagonists through modulation of atropisomer interconversion properties." J. Med. Chem. 2004, 47, 519-529.	
2046	Veenstra S.J. et al., "Studies on the active conformation of NK1 antagonist CGP 49823. Part 1. Synthesis of conformationally restricted analogs," Bioorganic & Medicinal Chemistry Letters, 7(3): 347-350 (1997)	
2047	Goldstein D.J. et al., "Lanepitant, an NK-1 antagonist, in migraine prevention," Cephalalgia, 2001 Mar; 21(2):102-6	
2048	George D.T. et al. "Neurokinin 1 Receptor Antagonism as a possible therapy for alcoholism," Science 319: 1536-1539 (2008)	
2049	Fujii, T. et al., "Pharmacological profile of a high affinity dipeptide NK1 receptor antagonist, FK888," Br. J. Pharmacol. 107:785-789 (1992)	
2050	Diemunsch, Pierre, and Laurent Grélot, "Potential of substance P antagonists as antiemetics," Drugs 60(3): 533-546 (2000)	
2051	Diemunsch, P. et al., "Neurokinin-1 receptor antagonists in the prevention of postoperative nausea and vomiting." British Journal of Anaesthesia, 103(1): 7-13 (2009)	
2052	Rosso, M. et al. "The NK-1 receptor is expressed in human primary gastric and colon adenocarcinomas and is involved in the antitumor action of L-733,060 and the mitogenic action of substance P on human gastrointestinal cancer cell lines." Tumor Biol. 29(4): 245-254 (2008)	
2053	Cascieri, M. et al. "Characterization of the binding and activity of a high affinity, pseudoirreversible morpholino tachykinin NK1 receptor antagonist." European Journal of Pharmacology 325(2-3): 253-26 (1997)	
2054	Sindrup, S. et al., "The NK1-receptor antagonist TKA731 in painful diabetic neuropathy: a randomised, controlled trial." European Journal of Pain 10(6): 567-571 (2006)	

Exhibit No.	Description	Previously Submitted?
2055	Vendruscolo, F. et al. "Evaluation of the anxiolytic-like effect of NKP608, a NK1-receptor antagonist, in two rat strains that differ in anxiety-related behaviors." Psychopharmacology 170(3): 287-293 (2003)	
2056	Saito, R. et al. "Anti-emetic effects of a novel NK-1 receptor antagonist HSP-117 in ferrets." Neuroscience letters 254(3): 169-172 (1998)	
2057	Ebner, K. et al., "Tachykinin receptors as therapeutic targets in stress-related disorders," Current Pharmaceutical Design 15(14): 1647-1674 (2009)	
2058	Shishido, Y. et al. "Discovery and stereoselective synthesis of the novel isochroman neurokinin-1 receptor antagonist 'CJ-17,493'." Bioorganic & Medicinal Chemistry 16(15): 7193-7205 (2008)	
2059	De la Puente-Redondo, V. et al. "The neurokinin-1 antagonist activity of maropitant, an antiemetic drug for dogs, in a gerbil model." Journal of Veterinary Pharmacology and Therapeutics 30(4): 281-287 (2007)	
2060	Rudd, J et al., "Inhibition of emesis by tachykinin NK1 receptor antagonists in Suncus murinus (house musk shrew)." European Journal of Pharmacology 366(2-3): 243-252 (1999)	
2061	Quartara, Laura and Altamura, Maria, "Tachykinin receptors antagonists: from research to clinic." Current Drug Targets 7(8): 975-992 (2006)	
2062	Emonds-Alt, Xavier et al. "SSR240600 [(R)-2-(1-{2-[4-{2-[3, 5-Bis (trifluoromethyl) phenyl] acetyl}-2-(3, 4-dichlorophenyl)-2-morpholinyl] ethyl}-4-piperidinyl)-2-methylpropanamide], a Centrally Active Nonpeptide Antagonist of the Tachykinin Neurokinin-1 Receptor: I. Biochemical and Pharmacological Characterization." The Journal of Pharmacology and Experimental Therapeutics 303(3): 1171-1179 (2002)	

Exhibit No.	Description	Previously Submitted?
2063	Shue, H. et al. "Cyclic urea derivatives as potent NK1 selective antagonists." Bioorganic & Medicinal Chemistry Letters 15(17): 3896-3899 (2005)	
2064	Araya, I. et al. "Process development and large-scale synthesis of NK1 antagonist." Chemical and Pharmaceutical Bulletin 56(2): 176-180 (2008)	
2065	Hesse, C. et al. "Kinetics and dynamics of the peripheral neurokinin-1 receptor antagonist SLV317 in healthy individuals." *British Journal of Clinical Pharmacology* 61(4): 414-419 (2006)	
2066	Megens AA, Ashton D, Vermeire JC, Vermote PC, Hens KA, Hillen LC, Fransen JF, Mahieu M, Heylen L, Leysen JE, Jurzak MR, Janssens F. Pharmacological profile of (2R-trans)-4-[1-[3,5-bis(trifluoromethyl)benzoyl]-2-(phenylmethyl)-4-piperidinyl]-N-(2,6-dimethylphenyl)-1-acetamide (S)-Hydroxybutanedioate (R116301), an orally and centrally active neurokinin-1 receptor antagonist. J Pharmacol Exp Ther. 302(2):696-709 (2002 Aug)	