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 ERIC ROELAND, M.D., FASCO, FAAHPM

Table of Contents

I. INTRODUCTION 1

II. BACKGROUND AND QUALIFICATIONS 4

III. MATERIALS REVIEWED 9

IV. LEVEL OF ORDINARY SKILL 10

V. STATE OF THE ART AT THE TIME OF THE INVENTION 12

A. Chemotherapy-Induced Nausea and Vomiting 12

1. Chemotherapy-Induced Nausea and Vomiting Are Two Different Adverse Effects 14

2. Detrimental Impact of CINV on Patients with Cancer 15

3. The Insidious Nature of Delayed Nausea 18

4. Classification Systems for Chemotherapeutic Agents and the Phases of Chemotherapy-Induced Nausea and Vomiting 22

B. State of CINV Treatments in November of 2009 26

1. "Complete Response" Endpoint 27

2. Standard Therapy 33

3. Triple Therapy (Standard Therapy + Aprepitant) 35

4. Pathophysiology of CINV Was Not Well Understood 37

5. CINV Treatments had Mechanisms of Action that were Not Well Understood 42

C. Various Drug Candidates Showed Potential for Controlling Chemotherapy-Induced Nausea in November 2009 46

1. Olanzapine 47

2. Gabapentin 49

3. Cannabinoids 50

4. Metoclopramide 52

5. Phenothiazines (Prochlorperazine/Promethazine) 53

VI. ANALYSIS OF CERTAIN LITERATURE CITED DR. PEROUTKA 55

A. Prior Art Shows Aprepitant Was Not Effective Against Nausea, and NK-1 Receptor Antagonists Were Unlikely to Treat Nausea 55

1. Herrstedt (Ex. 1010) 57

2. The 2008 Emend® Label (Ex. 1030), the 2003 Emend® Label (Ex. 2016), and the Poli-Bigelli Reference (Ex. 1039) 59

3. Campos (Ex. 1023) 77

4. Herrington (Ex. 1016) 84

5. Warr (Ex. 1034) 87

6. Hesketh (Ex. 1037) 90

7. Schmoll (Ex. 2073) 94

8. Yeo (Ex. 1048) 97

B. The Prior Art Provides Insufficient Data on NK-1 Receptor Antagonists as a Class and Netupitant in Particular 102

1. High Failure Rate of NK-1 Receptor Antagonists 103

2. Hargreaves (Ex. 1012) 105

3. Bös (Ex. 1014) 110

VII. CLAIM CONSTRUCTION 114

A. Claims Require Treating Chemotherapy-Induced Nausea to a Statistically Significant Degree Relative to Baseline 114

VIII. REBUTTAL TO DR. PEROUTKA'S OPINIONS.....119

A. The Cited References Do Not Disclose All of the Limitations 120

B. Dr. Peroutka's Analysis Fails to Consider Factors That Would Have Been Pertinent to a POSA 130

1. Dr. Peroutka Fails to Consider the Problem Facing a POSA.....131

2. Dr. Peroutka Fails to Analyze the Various Paths a POSA Could Have Taken To Find an Improved Treatment for Nausea 133

C. Dr. Peroutka Fails to Show a POSA Would Have Been Motivated to Select Netupitant for Use in Triple Therapy 141

1. Dr. Peroutka Fails to Show that a POSA Would Consider Netupitant as Equivalent to or an Improvement over Aprepitant.....142

2. Dr. Peroutka Did Not Explain Why a POSA Would Have Selected Netupitant from Among Other NK-1 Receptor Antagonists with Pre-Clinical Data.....149

D. Dr. Peroutka Fails to Show that a POSA Would Have Reasonably Expected that Substituting Netupitant for Aprepitant in Triple Therapy Would Have Successfully Improved Nausea Control 157

1. Dr. Peroutka's Reliance on Aprepitant Data Is Insufficient.....158

2. Dr. Peroutka Did Not Consider the High Failure Rate of NK-1 Receptor Antagonists.....165

3. Dr. Peroutka Fails to Show that There was an Expectation that a Single Dose of Netupitant would Prevent or Reduce the Severity of Nausea 166

IX. OBJECTIVE INDICIA.....166

A. Nexus.....167

B. Unexpected Results and Skepticism 171

X. CONCLUSION 179

I, Eric Roeland, M.D., FASCO, FAAHPM, declare as follows:

I. INTRODUCTION

1. I am a medical oncologist and palliative care specialist. My clinical practice focuses on caring for patients with cancer with poorly controlled symptoms. My research focuses on symptom science, a clinical research program dedicated to promoting the discovery, validation, and accessibility of innovative approaches to improving the quality of life of people with cancer, guided by rigorous, evidence-based, collaborative research. The overall goal is to improve treatment tolerance and quality of life of patients with symptomatic cancer, including chemotherapy-induced nausea and vomiting ("CINV"). I have practiced in the field of oncology for over 17 years. Currently, I see about 15-25 patients per week in the outpatient setting, but when I cover the inpatient setting, it could be upwards of 50 patients a week.

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

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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.

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 (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. I likewise understand that Dr. Peroutka was subsequently deposed regarding his declaration and Azurity’s assertions (“Peroutka Deposition Transcript”) (Ex. 2086).

4. I have been asked to provide my opinions on, among other things, 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 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]

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 $600/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.

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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.

II. BACKGROUND AND QUALIFICATIONS

8. As explained at the beginning of this Declaration, I have been a practicing medical oncologist and palliative care specialist since 2009.

9. My educational background includes an M.D. from the University of Colorado (2005). I completed a postdoctoral residency in internal medicine at the University of California (UC) San Diego (2005-2008). I completed a fellowship in Hospice and Palliative Medicine at San Diego Hospice and the Institute for Palliative Medicine (Symptom Management) (2008-2009), followed by a fellowship in Hematology and Oncology at UC San Diego (2009-2012). Only a small percentage of medical oncologists are dual-trained with fellowships in both oncology and palliative care in the United States.

10. I have held medical licenses in California (2007-2018), Massachusetts (2018-2022), Oregon (2021-2027), and Washington (2023-2025). I have received certifications from the American Board of Internal Medicine in Internal Medicine (2008-2018), Hospice and Palliative Medicine (2011-present), and Medical Oncology (2014-present). I participate in the Maintenance of Certification for both Hospice and Palliative Medicine and Medical Oncology through the American Board of Internal Medicine.

11. I have been appointed to several hospital positions. I was appointed as an Assistant Clinical Professor (2012-2018) at UC San Diego, Assistant in

Medicine (2018-2021) at Massachusetts General Hospital, and Assistant Professor (2021-2023) and Associate Professor (2023-present) at Oregon Health and Science University. Furthermore, I was appointed Director of Symptom Science at the Oregon Health and Science University Knight Cancer Institute (2021-present).

12. Across these healthcare systems, I have personal experience in prescribing oral and intravenous (IV) formulations of antiemetics used to treat CINV, including aprepitant, palonosetron, and netupitant/palonosetron.

13. I have also been appointed to several academic faculty positions. I was an Assistant Professor in Medicine in Hematology/Oncology at UC San Diego (2012-2018), Harvard Medical School (2018-2021), and Oregon Health and Science University (2021-2023). I am currently an Associate Professor in Medicine in Hematology/Oncology at Oregon Health and Science University (2023-present).

14. Through my work, I have been recognized as a key opinion leader in symptom control research, including nausea and vomiting. I have been involved in more than 30 clinical studies, both national and local, and I am an author of over 100 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 Napo Pharmaceuticals, AIM Specialty Health, Oragenics,

BASF, Immuneering, Vector Oncology, Asahi Kasei, Mitobridge, Actimed, Agilix, MeterHealth, Pfizer, Heron Therapeutics, and Aveo Pharmaceuticals. I also have served as an Ad Hoc Reviewer for the following journals: *Nature Medicine, British Medical Journal*, *Annals of Oncology*, *Journal of Clinical Oncology*, *JAMA Oncology*, *Journal of the National Comprehensive Cancer Network: JNCCN*, *Cancer*, *The Oncologist*, *British Journal of Nutrition*, *Journal of Geriatric Oncology*, *Supportive Care in Cancer*, *Psycho-Oncology*, *JCO Oncology Practice*, *Leukemia and Lymphoma*, *Journal of Pain and Symptom Management*, *Journal of Palliative Medicine*, *European Journal of Cancer Care*, and *Journal of Opioid Management*. Additionally, I was an Associate Editor of the *Journal of Supportive Care in Cancer* (2021-2023), Section Editor of the *New England Journal of Medicine Knowledge Plus* (*NEJM+*) for Oncology and Pain Management and Opioids (2023-2025), and Section Editor for UpToDate on Symptom Science and Palliative Care (2025-present).

15. Further, some of my writings have served as key curriculum in developing international standards for symptom management in medical oncology. For example, I wrote the chapter for the American Society of Clinical Oncology Self Evaluation Program (ASCO-SEP 2020) on "Pain and Symptom Management." This book is the key reference for all medical oncologists and advanced practice providers preparing to study for their medical oncology board exam. Moreover, I

was selected to develop a global curriculum in medical oncology specific to the management of systemic therapy toxicities and nutritional support in a combined effort of the American Society of Clinical Oncology and the European Society of Medical Oncology.

16. I have given over 50 invited lectures, including topics relating to CINV, clinical guidelines, and evidence-based symptom management. In particular, I was invited by the Food and Drug Administration ("FDA") as a panelist and discussant. These topics included the "Multidisciplinary Approach to Diarrhea Prevention and Management in the Cancer Patient" (Dec. 2017) and the "Cancer Cachexia Mini-Symposium" (Apr. 2020). I was also selected as an FDA and American Association for Cancer Research (AACR) Oncology Educational Fellow (2023-2024).

17. I am an active member of several professional societies. For example, I am a member of the American Society of Clinical Oncology (ASCO), Alliance for Clinical Trials in Oncology, Multinational Association of Supportive Care in Cancer (MASCC), and American Academy of Hospice and Palliative Medicine (AAHPM), among others. Previously, I was also engaged in the National Comprehensive Cancer Network (NCCN) while at UC San Diego and Massachusetts General Hospital, and National Cancer Institute. As a member of ASCO, NCCN, and MASCC, I contributed to the published evidence-based

guidelines that describe the best practices (standard of care) for treating CINV. MASCC is responsible for all of the supportive care guidelines in cancer for the European Society of Medical Oncology used worldwide, including CINV guidelines. I have also been recognized as a Fellow of AAHPM (2015-present) and a Fellow of ASCO (2023-present).

18. Specifically, for NCCN, I served as a member of the Antiemesis Panel (2013-2021). For ASCO, I have served in the following roles: Supportive Guidelines Member (2015-2017), Supportive Guidelines Co-Chair (2018-2021), Supportive Care in Oncology Symposium Planning Committee Co-Chair (2019), and Evidence-Based Guidelines Committee Member (2021-2025), Annual Meeting Scientific Program Committee Symptom Science and Palliative Care Track Member (2023-2026) and Chair (2024-2025). Currently, for ASCO, I serve as the Chair of the Evidence-Based Medicine Committee (2025-2026) that critically assesses all clinical practice guidelines (~200 total), including all supportive care guidelines, prior to their publication in the *Journal of Clinical Oncology*. These guidelines define the standard of care within oncology care across the United States. For the Alliance for Clinical Trials in Oncology (one of four cooperative groups of the National Cancer Institute-sponsored National Clinical Trials Network), I have served on the Symptom Intervention Committee (2011-2020) since my fellowship training and now serve as a Vice Chair (2021-present). I have

also served as a technical expert and reviewer for the Agency for Healthcare Research and Quality (AHRQ), including evidence-based guidelines for *Breathlessness in Patients with Advanced Cancer*, *Radiation Therapy for Bone Metastases*, and *Nutrition as Prevention for Improved Cancer Health Outcomes*.

19. I have volunteered with numerous patient advocacy groups, including the American Cancer Society, Lungevity, Pancreatic Cancer Action Network, Cancer Support Community, Cure Ocular Melanoma, and F!ght Colorectal Cancer.

20. My qualifications, professional experience, education, and publications are set forth in my *curriculum vitae*, which is being submitted as Ex. 2087.

III. MATERIALS REVIEWED

21. 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.

22. I have reviewed Dr. Navari's declaration and the opinions set forth therein. I have incorporated several portions of his declaration as they were relevant to my analysis and the opinions I have set forth in this declaration.

23. My opinions are also guided by my appreciation of what a POSA (as that term is discussed below in Section IV) 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, which is mentioned on the cover of the '357 patent.

IV. LEVEL OF ORDINARY SKILL

24. 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 in November 2009. I further understand that a POSA is presumed to be aware of all the pertinent prior art. In my opinion, the relevant field of invention is supportive cancer care. Supportive cancer care is, in general, the prevention, control, and management of the adverse effects of cancer and its treatment.

25. In my opinion, a POSA in November 2009 was actively involved in oncology with supportive cancer care, a field that spans multiple disciplines and requires collaborative teamwork among individuals 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.*, supportive cancer care) with at least three years of experience in the treatment of nausea and vomiting with supportive cancer care medications in patients with cancer undergoing chemotherapy. In this definition of

a POSA, more education can substitute for less practical experience, and vice versa.

26. 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.

27. I understand that Dr. Peroutka proposes a different definition of a POSA. Under Dr. Peroutka’s definition, a POSA would **not** need to have any experience with either the treatment of side-effects caused by chemotherapy (*e.g.*, chemotherapy-induced nausea (“CIN”), chemotherapy-induced vomiting (“CIV”), fatigue, and infections) or the medications commonly utilized in the field of supportive cancer care (*e.g.*, corticosteroids, neurokinin-1 (“NK-1”) receptor antagonists, serotonin 5-hydroxytryptamine-3 (“5-HT_3”) receptor antagonists, and dopamine receptor antagonists). (Ex. 1009 at ¶¶ 59-60.) However, a POSA would need clinical experience in supportive cancer care because without such experience, a POSA would not have a true appreciation of issues at the heart of the ’357 patent, namely, drug regimens for treating the side-effects of chemotherapy, like nausea and vomiting. Clinical experience in supportive cancer care would allow a POSA to understand the standard of care at the time of the

invention in November 2009, the types of challenges and shortcomings associated with that standard of care, and what solutions a POSA would have considered for solving those problems.

28. Therefore, I disagree with Dr. Peroutka's definition, because I believe his definition is overly broad and not directed to the subject matter of the invention, *i.e.*, supportive cancer care and particularly methods of treating 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.

29. I have significant expertise in the fields of oncology and supportive cancer care. Over the course of my career, I have instructed numerous students and supervised many junior clinicians. 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 do.

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

A. Chemotherapy-Induced Nausea and Vomiting

30. "Chemotherapy" is a systemic type of drug therapy that introduces cytotoxic agents into the bloodstream to damage and hopefully kill cancer cells. Unfortunately, chemotherapy also causes off-target damage to normal, healthy cells that are particularly sensitive to cytotoxicity, such as the cells in the bone marrow, digestive tract, and hair follicles. This collateral damage to non-cancerous

cells results in chemotherapy agents being associated with a range of severe adverse effects. These effects typically persist for days post-chemotherapy and greatly hinder the daily lives of patients, which in turn is often profoundly demoralizing. Two of the debilitating and common adverse effects associated with chemotherapy are (1) nausea and (2) vomiting (*i.e.,* emesis). (*See, e.g.*, Ex. 1010 at 143; Ex. 2001 at 1856.)

31. "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. (*See* Ex. 2036 at 517.) Two measures of nausea are commonly used in clinical studies: the Visual Analogue Scale ("VAS") and the Likert scale. On the other hand, "vomiting" (also known as "emesis")[3] is readily recognized and may consist of a pre-ejection phase (called "retching")

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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. (*See* Ex. 2074 at 230 (defining emesis as vomiting), 767 ("Vomiting means the expulsion of the stomach contents through the mouth. When the effort of vomiting is made, but nothing is brought up, the process is known as retching.").)

followed by ejection of stomach contents. (*See* Ex. 2036 at 517; Ex. 2086 at 38:8-39:24.)

1. Chemotherapy-Induced Nausea and Vomiting Are Two Different Adverse Effects

32. Nausea and vomiting each constitute a separate and distinct adverse event caused by cancer treatment. (*See* Ex. 1010 at 143; Ex. 2086 at 38:8-39:24.) The sensation of chemotherapy-induced nausea and the act of chemotherapy-induced vomiting, however, typically present as interrelated symptoms and thus are often referred to collectively (and sometimes imprecisely) as "chemotherapy-induced nausea and vomiting" ("CINV"). (*See, e.g.*, Ex. 2036 at 517, 528; Ex. 1010 at 143; Ex. 1039 at 3091; Ex. 2086 at 38:8-39:24.) But importantly, the sensation of nausea and the act of vomiting are protective reflexes with overlapping but distinct physiological pathways that work together to rid the stomach and intestines of toxic substances. (*See* Ex. 2036 at 517.)

33. Nausea and vomiting do not always coexist simultaneously, as one can experience nausea without vomiting, and one can also suddenly vomit without nausea. (*See* Ex. 2036 at 517; Ex. 2086 at 39:25-40:3.) This distinction between nausea and vomiting is important because, as I discuss later in this declaration (*see* Section V.B), in November 2009, no such treatment existed to treat both nausea and vomiting. While the standard of care "triple therapy" regimen (*i.e.*, a

combination of a corticosteroid (dexamethasone), a 5-HT_3 receptor antagonist, and aprepitant, further explained below in Section V.B.3) was effective in preventing vomiting after chemotherapy administration, it failed to provide meaningful control of nausea, including delayed nausea (*i.e.*, nausea occurring 24-120 hours after the administration of chemotherapy).

2. Detrimental Impact of CINV on Patients with Cancer

34. Historically, patients have ranked chemotherapy-induced nausea and chemotherapy-induced vomiting as "two of the worst adverse effects of cancer chemotherapy." (Ex. 1010 at 143; *see id.* at 148.) While approximately 70% to 80% of all patients undergoing chemotherapy experience nausea and/or vomiting, patients tend to experience nausea more frequently than vomiting. (*See* Ex. 2037 at 573.)

35. Collectively, unaddressed CINV symptoms not only decrease the quality of life of patients with cancer, but may also affect patient willingness to continue chemotherapy treatment, treatment intensity (dose reductions and delays), and healthcare utilization (*e.g.*, unscheduled hydration, emergency department visits, unplanned hospitalizations). (*See* Ex. 2036 at 516; Ex. 2001 at 1856.) CINV also results in significant morbidity. (Ex. 2036 at 516; *see also* Ex. 2001 at 1856; 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 esophageal tears, decline in behavioral and mental status, and wound dehiscence (openings). (Ex. 2036 at 516; Ex. 2001 at 1856; Ex. 2037 at 572.) Consequently, CINV may result in non-adherence to, dose reductions in, or even withdrawal from chemotherapy treatments for treatable cancers with positive historical clinical outcomes. (Ex. 2036 at 516; Ex. 2037 at 572; *see* Ex. 2001 at 1856.) In other words, patients may potentially die from cancer as a result of not being able to bear the side effects caused by chemotherapy.

36. However, following the development of 5-HT_3 receptor antagonists and aprepitant, patients receiving anti-emetic prophylaxis, for example, according to the 2004 MASCC guidelines, were often able to receive some relief from vomiting during the first 1-3 courses of chemotherapy. (Ex. 1010 at 143, 148.)[4]

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[4] An "antagonist" is a chemical compound administered to block other molecules from binding to their receptors, preventing the effect of the transmitters released. (*See* 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." Similarly, a 5-HT_3 receptor antagonist is a chemical compound that blocks or inhibits another molecule from binding to the 5-HT_3 receptor.

As a result, the majority of patients in November of 2009 considered nausea to be the worst adverse effect of chemotherapy treatment, and loss of appetite replaced vomiting as chemotherapy's second worst adverse effect. (*See* Ex. 1010 at 143, 148 ("Nausea and loss of appetite are the main problems for the majority of patients."); *see, e.g.*, Ex. 2036 at 517, 528; Ex. 2001 at 1874.) Stated a different way, the majority of patients considered chemotherapy-induced nausea to be worse than other common side effects of chemotherapy, including:

- Vomiting
- Fatigue
- Hair loss
- Thrombocytopenia (low platelet count)
- Neutropenia (low white blood count)
- Increased risk of infection
- Anemia (low red blood cell count)
- Appetite changes
- Constipation
- Diarrhea
- Mouth sores
- Peripheral neuropathy or other nerve problems

- Skin and nail changes, such as rash, dry skin, and color change
- Bowel or bladder incontinence
- Weight changes
- "Chemo brain" (asthenia, cognitive decline in memory, concentration, focus)
- Anxiety
- Depression
- Changes in libido and sexual function
- Fertility problems

(*See, e.g.*, Ex. 1010 at 148; Ex. 2102 at 13-18; Ex. 2103 at 1056 (Tables 1 and 2).)

3. The Insidious Nature of Delayed Nausea

37. As of November 2009, nausea, especially delayed nausea (*i.e.*, nausea occurring >24 hours after administering chemotherapy), was considered the more challenging and resistant symptom for most patients. (*See, e.g.*, Ex. 1010 at 148 ("Nausea and loss of appetite are the main problems for the majority of patients"); Ex. 2001 at 1874 ("The control of nausea in patients receiving MEC and HEC remains a significant problem."); Ex. 2036 at 528 ("The control of nausea in patients receiving moderately and highly emetogenic chemotherapy remains a significant problem."); Ex. 2081 at 204 ("In spite of major improvements in controlling emesis after chemotherapy the effectiveness of the available antiemetic prophylaxis for nausea is still limited.").) Indeed, "the later portion of the acute

phase and the delayed phase [is] the period during which acute failures associated with standard therapy typically occur." (Ex. 1037 at 4117.) Accordingly, reducing delayed nausea is particularly important because "patients are protected at a time when they are especially vulnerable to failure of standard antiemetic therapy." (Ex. 1037 at 4117.)

38. The literature available in November 2009 consistently documented that nausea had a higher incidence, was more difficult to control, and had a greater effect on patients' quality of life as compared to vomiting. (*See, e.g.*, Ex. 2081 at 199; Ex. 2075 at 4472 ("[A]ntiemetic treatments have been less effective in improving delayed nausea and vomiting than acute nausea and vomiting."); Ex. 2037 at 587; Ex. 1034 at 2826-27, 2829 (aprepitant's impact on daily living did not make a significant difference in the nausea domain score).) While 5-HT_3 receptor antagonists combined with dexamethasone had achieved approximately 70% control of acute emesis by the early 2000s, about 40% of patients still experienced symptoms in the delayed phase, with delayed nausea being particularly problematic. (*See* Ex. 2081 at 199.) This patient-reported data is consistent with what the 2009 NCCN Antiemetic Guidelines reported, specifically that "40% of patients . . . still experienced significant nausea" whether they received triple therapy or standard therapy. (Ex. 2037 at 587 (citing Ex. 1034); *see also* Ex. 2075 at 4476 ("the rate of delayed nausea was unexpectedly similar after HEC and MEC

treatment (60.3% v. 52.4%, respectively).”).[5]) The NCCN guidelines provided a consensus of expert views on the accepted approaches to CINV treatment in 2009. (Ex. 2037.)

39. In my experience, there is a common misconception with nausea and vomiting among patients receiving chemotherapy. Patients living with cancer, at times, believe that nausea and vomiting are evidence that their chemotherapy is working. Based on this misunderstanding, patients will not report these chemotherapy side effects to their clinicians out of fear that their life-saving chemotherapy may be changed to a less aggressive treatment. This feeling in patients can explain the discordance between what patients experience and what physicians report.

40. Overall, patients experience more nausea and vomiting than reported by clinicians. In my experience, delayed nausea is particularly difficult to treat and especially detrimental to patients living with cancer. Delayed nausea can have the greatest detrimental impact on patients’ quality of life. If a patient experiences

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[5] “Triple therapy” and “standard therapy” are drug regimens administered to patients in advance of chemotherapy administration. I discuss them below in detail in Section V.B.

vomiting, it may be a single episode followed by a feeling of relief, whereas nausea is a persistent, uneasy feeling that lasts much longer.

41. In my experience, delayed nausea typically happens to patients outside of the hospital, when they are at home following chemotherapy. At that point, patients only have access to home-based oral regimens.[6] Patients experiencing nausea, however, often do not want to orally ingest anything, including food, water, and medications, given existing symptoms and fear that their nausea may worsen. Consequently, patients may become dehydrated, stop eating, and lose

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[6] When in the hospital or clinic setting, "[p]atients who cannot tolerate orally administered medications because of active mucositis, difficulty in swallowing or poor function of the [gastrointestinal (GI)] tract may require intravenous antiemetics prior to chemotherapy." (Ex. 2036 at 522.) Despite Dr. Peroutka's opinions to the contrary (Ex. 1009 at ¶ 138), IV prophylaxis to treat CINV is the most common route of administration throughout the United States with oral agents being used more commonly for breakthrough nausea and delayed/home dosing. The practical rationale for this fact is that single-visit administration ensures adherence and bioavailability, reducing missed doses that can occur with home-based oral regimens.

weight. For example, patients may report that they are not hungry or have no appetite, and to a clinician, this report could indicate that the patient is suffering from nausea. If the effects of nausea following chemotherapy are not managed properly, patients may require emergency department evaluation and even hospitalization due to dehydration and malnutrition. Furthermore, because many social interactions center on food, patients experiencing nausea may also withdraw socially.

42. Delayed nausea is harder to predict and treat and can insidiously erode a patient's willingness to continue therapy over repeated cycles. Therefore, even modest improvements in the control of delayed nausea represent a major advance, offering patients renewed tolerance for chemotherapy and giving clinicians a powerful tool to help them on potentially life-saving treatment.

4. Classification Systems for Chemotherapeutic Agents and the Phases of Chemotherapy-Induced Nausea and Vomiting

43. In November 2009, chemotherapeutic agents were classified by their emetic (not nausea) 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.)

44. Furthermore, 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).[7] (Ex. 2037 at 585-86; Ex. 2001 at 1856, 1860.) Antiemetic combinations are selected based on their mechanism of action, pharmacokinetics, and efficacy at different time points. (*See* Ex. 2037 at 573, 585-86; Ex. 2036 at 525-26.) For example, CINV clinical trials used various endpoints to

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[7] 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. (*See* 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," rescue therapy typically involves different drugs than the drugs that were used prophylactically. (*See* Ex. 2036 at 526.)

independently and specifically measure the occurrence of each side effect. I have summarized some of the endpoints used in the chart below:

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; Ex. 2036 at 518; Ex. 1010 at 143.)

45. As discussed further below, Section V.B.5, as of November 2009, the mechanisms of action between chemotherapy agents, the emetic reflex arch, and any related neurotransmitters were not well defined. (*See, e.g.*, Ex. 2036 at 517; Ex. 2037 at 573, 585; Ex. 1010 at 143; Ex. 1022 at 1446; Ex. 1034 at 2829; Ex. 1048 at 534.) Historically, chemotherapeutic agents were believed to cause CINV by activating certain neuroreceptors located in the central nervous system and gastrointestinal tract. (*See* Ex. 2037 at 573; Ex. 2036 at 517.) By November of 2009, various neuroreceptors had been identified as potentially being involved in

CINV, including serotonin, dopamine, neurokinin-1 (NK-1), acetylcholine, gamma-aminobutyric acid (GABA), histamine, cannabinoid, opioid, endorphin, and muscarinic. (*See* Ex. 2036 at 517-18, 524; Ex. 2037 at 573.) Some exemplary antiemetic agents include benzodiazepines, cannabinoids, corticosteroids, dopamine antagonists, NK-1 receptor antagonists, and 5-HT_3 receptor antagonists. (Ex. 2001 at 1872 (Table XII).) However, the prior art also repeatedly mentions that future studies will hopefully "provide new information on the mechanism of CINV," including a better understanding of which neurotransmitters, neuroreceptors, parts of the gastrointestinal ("GI") tract, and regions of the central nervous system ("CNS")[8] are specifically involved/important to each of the two side effects. (Ex. 2036 at 529; *see also* Ex. 1010 at 143; Ex. 1034 at 2829; Ex. 2037 at 585; Ex. 1022 at 1446 ("Serotonin antagonists are believed to be effective in acute CINV" but "[o]ther factors that may play a role in acute CINV in humans are less well understood" and "the exact mechanism of delayed CINV, especially in humans, is not well understood.").)

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[8] The CNS consists primarily of the brain, brain stem, spinal cord, and retina.

B. State of CINV Treatments in November of 2009

46. In November of 2009, developing treatments for CINV in general, and for chemotherapy-induced nausea in particular, was a highly complicated and unpredictable art for a multitude of reasons, including:

- CINV clinical trials used a vetted primary endpoint of "complete response" to establish efficacy (Section V.B.1)
- CINV's etiology and pathophysiology were not well understood (Section V.B.4)
- CINV treatments had mechanisms of action that were not well understood (Section V.B.5)
- High failure rate of NK-1 receptor antagonists, especially in treating nausea in the delayed phase (Section VI.B.1)
- Nausea is an inherently subjective adverse event and is difficult to quantify from patient to patient (*See generally* Section VIII.C.1.)

47. In November 2009, sponsors developing drugs for the prevention of CINV almost exclusively used the primary efficacy endpoint of "complete response" – defined as no vomiting and no use of rescue antiemetic medication – when conducting clinical trials for a drug's efficacy against CINV, and ultimately, its approval by the FDA with a CINV indication. (*See also* Ex. 2001 at 1860, 1874.) The treatment guidelines for the prevention of CINV, published by

November 2009, recommended the administration of a three-drug regimen that combined dexamethasone, a 5-HT_3 receptor antagonist, and the NK-1 receptor antagonist aprepitant. (Ex. 2037 at 575.) 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.*, ondansetron, granisetron, palonosetron), and (3) the NK-1 receptor antagonist aprepitant. (Ex. 2036 at 521.) Prior to the use of "triple therapy" for treating CINV, clinicians used "standard therapy" for treatment of CINV, which was a two-drug regimen involving a corticosteroid (mainly dexamethasone) and a 5-HT_3 receptor antagonist. (Ex. 2036 at 521.)

48. I discuss each of these topics in detail below. All these factors contributed to the highly unpredictable nature of developing a new CINV treatment that was safe and effective (let alone effective against chemotherapy-induced nausea) in 2009. Indeed, many of these factors persist today and continue to challenge the development of new CINV treatments.

1. "Complete Response" Endpoint

49. For context, there are three hierarchies of endpoints that are used in clinical studies. The first type is "primary endpoints" which are critical to establish effectiveness for approval. (*See* Ex. 2076 at 6-7.) The second type is "secondary

endpoints" which can provide useful information to support the primary endpoint(s) and/or demonstrate additional clinically relevant effects. (*See* Ex. 2076 at 7.) The third type is "exploratory endpoints" which can include endpoints for research purposes or for new hypotheses generation. (*See* Ex. 2076 at 3, 5, 34.)

50. In addition, endpoints can also be described in terms of the number of components that they represent. "Single-component" endpoints refer to a clinical endpoint that measures a single event or outcome, such as death. "Composite endpoints" combine multiple single endpoints into a single outcome. The treatment effect on the composite event rate can be interpreted as characterizing the overall clinical effect when the individual events all have reasonably similar clinical importance. Importantly, the composite endpoint's effect may not reflect the effects of the individual components – or accurately describe the drug's benefit – if the components vary substantially in clinical importance and the observed treatment effect is driven mainly by the least important event. Furthermore, the overall outcome may still yield a favorable statistical result, even if a more important component is adversely affected by the treatment, which could then raise doubt about the treatment's clinical value. In that case, although the overall statistical analysis indicates the treatment is beneficial, careful examination of the data could call this conclusion into question. For this reason, as well as for a greater depth of understanding of the treatment's effects, analyses of the individual

components of the composite endpoint are important and can influence the interpretation of the overall study results.

51. Below, I have copied Table IV from a 2009 review article, which summarizes the various efficacy endpoints that were used in aprepitant's Phase III trials, and denote the single-component endpoints with blue highlights and the composite endpoints with green highlights:

Table IV. Efficacy endpoints for randomized, double-blind, phase III trials involving aprepitant regimens used in the prevention of nausea and vomiting in patients receiving chemotherapy or post-operatively in patients who have undergone surgery

Endpoint	Definition
No emesis	No vomiting (oral expulsion of stomach contents), retching or dry heaves (an attempt to vomit that is not productive of stomach contents) regardless of use of rescue medication
No rescue therapy	No use of medication to treat established nausea or emesis
No nausea	Maximum nausea VAS rating <5 mm
No significant nausea	Maximum nausea VAS rating <25 mm
Complete response	No emesis (or no vomiting) and no rescue therapy
Complete protection	No emesis (or no vomiting), no rescue therapy, no significant nausea
The impact of CINV on daily life	FLIE[26] total score >108 out of a maximum possible score of 126

CINV = chemotherapy-induced nausea and vomiting; **FLIE** = Functional Living Index Emesis; **VAS** = visual analog scale from 0 ('no nausea') to 100 mm ('worst possible nausea').

(Ex. 2001 at 1860, Table IV (annotations added).)

52. The use of composite endpoints in the aprepitant clinical studies attempted to summarize the patient's experience of CINV as a single endpoint. The following are some examples of composite endpoints that were used over the acute, delayed, and overall phases of CINV in clinical studies as of November 2009 to assess the efficacy of a given drug candidate:

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

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

53. In my experience, the primary endpoint of "complete response" is often used in clinical trials because it is a binary measurable endpoint: whether a patient vomited (or not) or used rescue antiemetics (or not). The "complete response" endpoint, however, does not include nausea as a stated parameter. Instead, a complete response only measures the ability to control vomiting. (*See* Ex. 1010 at 148; Ex. 2036 at 521-22.) For example, aprepitant (*see* Section VI.A) is approved for treating CINV, but does not control nausea to a significant degree

in a significant number of patients. (Ex. 2036 at 521-22, 528; Ex. 1010 at 143, 148.)

54. When a composite endpoint is used as a primary endpoint, the individual components of that composite endpoint should also be analyzed separately as secondary endpoints, provided they are clinically meaningful and validated. (Ex. 2076 at 7.) Secondary variables are either supportive measurements related to the primary objective or effect measurements related to secondary objectives. Another issue with clinical trials that use composite endpoints like "overall complete response" is that improvements that occurred only in the acute or delayed phase of CINV could have a larger effect in one phase that drives the overall result. (*See* Ex. 2036 at 522.)

55. In my experience, very few studies in November 2009 used nausea as a primary endpoint, given that nausea is a patient-reported symptom that is difficult to measure. Instead, studies preferred to use the endpoint of vomiting, which is an objective, well-defined event that is easily measured. Studies typically relied on less definitive secondary composite endpoints to indirectly assess control of nausea, for example, the composite endpoint of "complete protection" that includes "no significant nausea," though best practice would be to rely on the component endpoint of "no significant nausea" itself. (*See, e.g.*, Ex. 1037 at 4115-16; Ex. 1039 at 3092, 3095.) One notable exception was the casopitant Phase 2 trial

published in 2009, which included "no significant nausea" (≥25 mm on a visual analog scale) as a co-primary endpoint alongside "complete response." (Ex. 2095 at 5807.) This approach was unusual for the era. Notably, the trial found that rates of no significant nausea did not differ among treatment arms (range 28-29%), highlighting that casopitant – like aprepitant – had difficulty in demonstrating nausea control when measured as a primary outcome. (*Id.* at 5807-08.)

56. In addition to determining numerical values for the different endpoints, clinical studies will often evaluate "statistical significance," which is denoted by the term "p-value." A POSA would have understood that statistical significance is important because it minimizes the chances of a false favorable conclusion for any primary or secondary endpoints. (*See* Ex. 2085 at 5, n.5.) The p-value refers to the probability of concluding that there is a difference (beneficial or harmful) between the drug and a defined "control"[9] (or baseline) when there is

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[9] In order to evaluate statistical significance, controls are used to establish a baseline for comparison, ensuring the observed effects are caused by the independent variable, rather than chance. For example, in evaluating a regimen of a dexamethasone, a 5-HT_3 receptor antagonist, and an NK-1 receptor antagonist

actually no difference. For example, a p-value of 0.05 means that the probability of falsely concluding that the drug differs from the control in either direction (benefit or harm) when no actual difference exists is no more than 5% (or 1 chance in 20). Relying solely on the statistically significant primary and secondary endpoints of a clinical trial ensures that the major findings are well supported and that the drug's effects have been demonstrated.

2. Standard Therapy

57. Prior to aprepitant, clinicians treated CINV with "standard therapy," which was a two-drug regimen involving a corticosteroid (mainly dexamethasone) and a 5-HT_3 receptor antagonist. (Ex. 2036 at 521.) Below, I briefly discuss what was known by November 2009 about each drug class and its respective mechanism of action as part of standard therapy.

a. Corticosteroids

58. The first drug class to have been recognized as useful for treating CINV was corticosteroids. The corticosteroid frequently recommended for use in standard therapy was dexamethasone, in large part due to its widespread use and

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(independent variable), a standard therapy regimen of dexamethasone and a 5-HT_3 receptor antagonist is used as a comparison to determine the effect of adding an NK-1 receptor antagonist.

prolonged biologic (pharmacodynamic) half-life (~36-72 hours). (*See, e.g.*, Ex. 1010 at 145; Ex. 2036 at 524.)

59. While studies had determined the optimal pre-chemotherapy dosages for dexamethasone, the optimal dose for the control of delayed emesis had not been determined. (*See* Ex. 2036 at 524.) Additionally, because "the doses of anti-emetics are defined in studies using emesis as the primary end-point . . . [i]t is therefore unknown if higher doses than recommended of for example corticosteroids increase the effect against nausea." (Ex. 1010 at 148.) However, clinical studies have also demonstrated that "[d]examethasone was significantly superior to placebo in terms of the percentage of patients free of delayed vomiting or moderate to severe nausea (87% compared with 77%; P <0.02)." (Ex. 1013 at 24.)

b. 5-HT_3 Receptor Antagonists

60. The second drug class in standard therapy was 5-HT_3 receptor antagonists. (*See* Ex. 2037 at 575.) In this context, an "antagonist" is a compound that is administered to block certain neurotransmitters from binding to their receptors. (Ex. 1010 at 144.) 5-HT_3 receptor antagonists were effective in preventing acute vomiting (<24 hours) because they blocked the serotonin receptors that rapidly respond to serotonin released from the gut in response to cytotoxic chemotherapy. (*See* Ex. 2036 at 518-19; Ex. 1010 at 144.) As of

November 2009, there were at least seven well known 5-HT_3 receptor antagonists: (1) azasetron, (2) dolasetron, (3) granisetron, (4) ondansetron, (5) ramosetron, (6) tropisetron, and (7) palonosetron.

61. After the discovery of 5-HT_3 receptor antagonists, but before NK-1 receptor antagonists started being used to treat CINV, the published CINV treatment guidelines focused primarily on vomiting. Specifically, they recommended the use of dexamethasone and a 5-HT_3 receptor antagonist pre-chemotherapy (Day 1) as standard therapy 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) to prevent delayed chemotherapy-induced vomiting. (Ex. 2036 at 518-19.)

3. Triple Therapy (Standard Therapy + Aprepitant)

62. By November 2009, "triple therapy" had been dubbed the "standard of care" or "gold standard" for treatment of CINV. (*See, e.g.*, Ex. 1022 at 1447.) "Triple therapy" was a three-drug combination regimen that consisted of the NK-1

receptor antagonist aprepitant[10] added to "standard therapy" of a 5-HT_3 receptor antagonist and dexamethasone. (Ex. 2036 at 521; *see also* Ex. 2086 at 62:12-24, 63:25:64:20.) Triple therapy resulted in improved control of acute, delayed, and overall emesis control as compared to standard therapy. (Ex. 2036 at 521.)

63. Yet, despite the fact that aprepitant improved the control of emesis, the "control of nausea was not improved with the use of aprepitant," and nausea control remained inferior to vomiting control. (Ex. 2036 at 522, 527 ("Aprepitant did not improve nausea in the study."); 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;

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[10] Aprepitant had two formulations, oral tablets of aprepitant marketed under the brand name Emend® (FDA approved in 2003) and an injectable prodrug of aprepitant (fosaprepitant dimeglumine), marketed as Emend® for Injection ("Emend® IV"; FDA approved 2008). (Ex. 2002; Ex. 2004.) When fosaprepitant is administered intravenously, it is converted to aprepitant within 30 minutes and provides a similar antiemetic effect. (Ex. 2036 at 522.)

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 ("there was no difference in the nausea domain").)

4. Pathophysiology of CINV Was Not Well Understood

64. I disagree with Dr. Peroutka's opinion regarding a POSA's understanding of CINV's pathophysiology, including the mechanisms of the emetic reflex arch and the related neurotransmitters. (*See, e.g.*, Ex. 1009 at ¶¶ 75-86.) Specifically, Dr. Peroutka opines that the prior art disclosed that the binding of substance P to the NK-1 receptor "triggers feelings of nausea and a vomiting reflex." (*Id*. at ¶ 77 (citing Ex. 1012, Ex. 1011, Ex. 1023).) For example, in the "Technical Background" section of his declaration, Dr. Peroutka opines that "[t]hose in the field understood Substance P, in particular, to play a role in many biological processes, such as . . . nausea, vomiting, and pain." (Ex. 1009 at ¶ 76 (citing Ex. 1011 (Hoffmann) at 1362; Ex. 1012 (Hargreaves) at 23; Ex. 1014 (Bös) at 1:23-67, 39:42-48; Ex. 1043 (Saito) at Abstract; Ex. 1023 (Campos) at 1760).) He further opines that drugs such as aprepitant and fosaprepitant "prevent substance P from binding to the NK_1 receptors, thereby blocking the activation of the vomiting reflex and preventing the associated nausea and vomiting." (*Id*. at ¶

77.) Dr. Peroutka, however, misstates the disclosures of his cited reference, as I discuss in the next paragraph. In November 2009, a POSA would have still considered CINV's pathophysiology to largely be a mystery. (*See, e.g.*, Ex. 1022 at 1446 ("Serotonin antagonists are believed to be effective in acute CINV" but "[o]ther factors that may play a role in acute CINV in humans are less well understood" and "the exact mechanism of delayed CINV, especially in humans, is not well understood."); Ex. 2073 at 1000 ("Whereas acute vomiting is known to depend primarily on serotonin, the pathophysiology of delayed vomiting is less well understood and multiple mechanisms may contribute.").)

65. None of the references cited by Dr. Peroutka support his contention that substance P plays a role in nausea. Instead, the references discuss the role of neurokinin NK-1 receptors in emesis. For example, Saito discloses that "some of the evidence suggest[s] the roles of substance P and its receptor, neurokinin NK_1 receptor, in the brainstem nuclei in the development of ***emesis***." (Ex. 1043 at Abstract (emphasis added); *see also* Ex. 1023 at 1760 ("Substance P is . . . found in neurons (including vagal afferent fibers) innervating the brainstem nucleus tractus solitarii and the area postrema. Both regions are intimately involved in the induction of ***vomiting***. Exogenous Substance P applied to cells in the nucleus tractus solitarii results in ***emesis***.") (emphasis added).) Furthermore, the prior art taught a POSA "that serotonin and substance P may play a relatively more

important role in the pathogenesis of vomiting than of nausea, and that other neurotransmitters may also be involved in the pathogenesis of these symptoms, especially nausea." (Ex. 1034 at 2829.) Likewise, a POSA at that time would have understood that the prior art discloses that the "use of aprepitant-based anti-emetic regimen . . . is active against vomiting induced by serotonin and substance P, while nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy." (Ex. 1048 at 534.)

66. But setting the disagreement that I describe above aside, Dr. Peroutka and I do appear to agree on the following key facts:

- Nausea and vomiting are two different side effects, and each has its own distinct physiological pathway and mechanism of action (*see, e.g.*, Ex. 2086 at 38:22-42:5, 210:20-211:1);
- The terms "emesis" and "vomiting" both refer to the same act of ejecting the stomach contents out of the mouth and are thus interchangeable (*see, e.g.*, Ex. 2086 at 39:17-24);
- "[T]he mechanisms for nausea are not completely known even today" (*see, e.g.*, Ex. 2086 at 38:25-39:3);
- "Within the body, the causes for nausea can be different than the causes for vomiting" (*see, e.g.*, Ex. 2086 at 41:24-42:1);

- It is possible that treatments that work for vomiting may not necessarily work for nausea (*see, e.g.*, Ex. 2086 at 42:2-5);
- "[I]t was known in the field that substance P may play a relatively more important role in the pathogenesis of vomiting as compared to nausea in the 2009 time period" (*see, e.g.*, Ex. 2086 at 209:24-210:3).

67. As of November 2009, a POSA would have understood that all three of the underlying mechanisms involved in CINV were not well-defined, *i.e.*, (1) nausea, (2) vomiting, and (3) chemotherapy's ability to induce nausea and vomiting. Indeed, the references available to a POSA at that time disclosed that neither the pathogenesis of vomiting nor that of nausea was well understood. (*See, e.g.*, Ex. 1010 at 143; Ex. 1034 at 2829; Ex. 2036 at 517-18; Ex. 2037 at 585.) For instance, "[t]he mechanisms of emesis are not well defined" (Ex. 2036 at 517) and "[a] final common pathway for emesis has not been identified" (Ex. 2037 at 585). (*See also*, Ex. 1010 at 143 ("The understanding of the emetic reflex arch is complicated and subject to current changes.").)

68. In addition, the references disclosed to a POSA that "[i]t is thought that chemotherapeutic agents cause vomiting by activating neurotransmitter receptors located in the [chemoreceptor trigger zone], GI tract and [vomiting center]," and "investigations suggest that . . . chemotherapy agents, or their metabolites in the blood or cerebrospinal fluid, may directly affect areas in the

medulla oblongata or may stimulate the GI tract via the vagus nerve to send impulses to the medulla." (Ex. 2036 at 517.) Moreover, the art at that time taught that the mechanisms for CINV occurring in the acute phase appears to be different for CINV occurring in the delayed phase, which adds yet another layer of unpredictability. (Ex. 2036 at 518; Ex. 1022 at 1446 ("Serotonin antagonists are believed to be effective in acute CINV" but "[o]ther factors that may play a role in acute CINV in humans are less well understood" and "the exact mechanism of delayed CINV, especially in humans, is not well understood.").) Accordingly, the prior art also repeatedly mentions that future studies will hopefully "provide new information on the mechanism of CINV," including a better understanding of which neurotransmitters, neuroreceptors, parts of the gastrointestinal (GI) tract, and regions of the central nervous system (CNS) are specifically involved and important to each of the two side effects. (*See, e.g.*, Ex. 2036 at 529; Ex. 1010 at 143; Ex. 1034 at 2829; Ex. 2037 at 585.)

69. Consequently, a POSA would have known that (contrary to Dr. Peroutka's oversimplification) while "emesis is a natural consequence of treatment with most cancer chemotherapy," "[t]he understanding of the emetic reflex arch is complicated and subject to current changes." (Ex. 1010 at 143.) Likewise, a POSA at the time would have been skeptical that substance P would play a role in

the pathogenesis of nausea such that the antagonism of NK-1 receptors would provide a significant effect against nausea. (*See, e.g.*, Ex. 1048 at 534.)

5. CINV Treatments had Mechanisms of Action that were Not Well Understood

70. The prior art teaches that "[t]he prevention of nausea and vomiting involves a complex interaction between multiple organs and multiple neurotransmitters," and that "[c]ontinued research is needed to provide the most effective antiemetic regimen," which "is likely to involve a combination of various antiemetic agents with different mechanisms of action." (Ex. 2001 at 1875.) In contrast to these disclosures at the relevant time, Dr. Peroutka opines that a POSA would have understood triple therapy to constitute a plug-and-play therapy that allowed for simply substituting any one compound for any other compound in the antiemetic combination therapy, just as long as both compounds were in the same drug class and were intended to achieve their purpose through the same mechanistic pathway. (*See, e.g.*, Ex. 1009 at ¶¶ 77, 997.) However, as with CINV itself, the mechanisms of action of the various antiemetic agents available in 2009 were also poorly understood. For example, the following summaries are based upon information from publications available to a POSA in 2009:

- **<u>Corticosteroids</u>:** The prior art available in November 2009 disclosed that "[t]he mechanism of action of the antiemetic effects of the corticosteroids is unknown. There are no data that suggest an active receptor of a site of action." (Ex. 2036 at 524.) "[H]ypotheses such as modification of the capillary permeability of the chemoreceptor trigger zone, decrease in the inflammatory changes in the gut and participation in the release of endorphins have been suggested." (Ex. 1010 at 144.)
- **<u>5-HT_3 receptor antagonists</u>:** The prior art available in November 2009 disclosed that serotonin antagonists were believed to be effective in acute CINV, because serotonin is released rapidly from the gastrointestinal tract in the first 24 hours to stimulate the chemoreceptor trigger zone in the central nervous system, resulting in nausea and vomiting. (*See* Ex. 1022 at 1446.) Efficacy against acute emesis was "believed to be due to a predominately peripheral site of action," which prevents stimulation by serotonin released from the gut by cytotoxic agents. (*See* Ex. 2036 at 518.) Conversely, the lack of efficacy against delayed emesis "may be due to the lack of central effect by the 5-HT_3 receptor antagonists." (Ex. 2036 at 518.)

- **<u>NK-1 receptor antagonist</u>:** The prior art available in November 2009 disclosed that "results suggest that NK-1 receptor antagonists may exert their main anti-emetic action by depressing the neural activity of the [nucleus tractus solitarius] neurons, with possibly some antiemetic effects from peripheral sites through a blockade of the NK-1 receptors located on the vagal terminals in the gut." (Ex. 2036 at 521.)
- **<u>Olanzapine</u>:** The prior art available in November 2009 disclosed that activity at multiple receptors, including dopamine at D_1, D_2, D_3 and D_4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3 and 5-HT_6 receptors, catecholamines at α_1-adrenergic receptors, acetylcholine at muscarinic receptors and histamine at H_1 receptors, which appear to be involved in nausea and emesis, suggests why olanzapine is a good antiemetic, but without clarifying which receptors are important. (*See* Ex 2036 at 524.)
- **<u>Gabapentin</u>:** The prior art available in November 2009 disclosed that gabapentin may reduce delayed nausea, but further studies would be necessary to determine the efficacy of this agent. (*See* Ex. 2036 at 525.)

- **<u>Cannabinoids</u>:** The prior art available in November 2009 disclosed that "[c]annabinoid CB_1 receptors are present in the area postrema, [nucleus tractus solitarius] and dorsal motor nucleus, which are key sites within the brainstem for emetogenic control. Recent evidence suggests that CB_2 receptors are present on brainstem neurons and may have a role in mediating the cannabinoids effects on emesis." (Ex. 2036 at 525.)

71. Additionally, in November 2009, "[l]ittle is known about why anti-emetics are ineffective in some patients."[11] (Ex. 1010 at 149.) "Further studies exploring the possibility of prescribing anti-emetics on a pharmacogenetic basis are needed." (Ex. 1010 at 149.)

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[11] In fact, "[r]ecognizing the rapid changes that can occur in the antiemetic field," the Multinational Association of Supportive Care in Cancer ("MASCC") guidelines "established a process for updating the guidelines every 6 months," hoping to "provide practitioners with timely evidence-based recommendations which will further minimize the extent of nausea and vomiting experienced by cancer patients." (Ex. 1013 at 27.)

C. Various Drug Candidates Showed Potential for Controlling Chemotherapy-Induced Nausea in November 2009

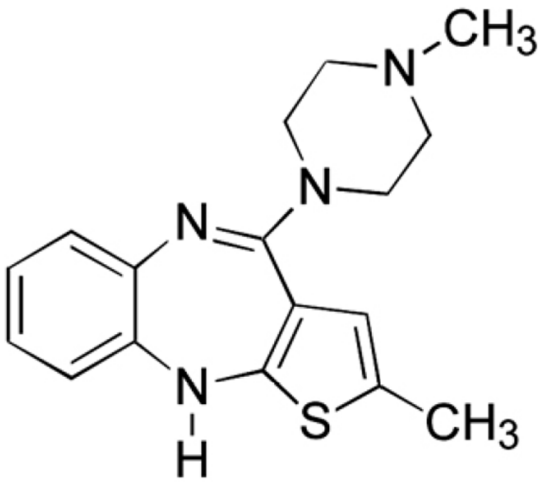
72. As of November 2009, the triple therapy had largely solved the problem of chemotherapy-induced vomiting (emesis) but had not solved the problem of chemotherapy-induced nausea, and a majority of patients still experienced nausea following chemotherapy and considered "nausea as the main problem." (Ex. 1010 at 143, 148; Ex. 2036 at 528.) At that time, numerous large clinical studies suggested that aprepitant in combination with dexamethasone and 5-HT_3 receptor antagonists (*e.g.*, ondansetron, palonosetron) significantly improved the prevention of vomiting, but had no significant effect on the control of nausea. (*See, e.g.*, Ex. 2036 at 527-29; Ex. 1034 at 2826-29; Ex. 1048 at 531-34; Section VI.A.) As a result, and unlike chemotherapy-induced vomiting, the control of chemotherapy-induced 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. 1048 at 531-34.).)

73. As of November 2009, numerous drug candidates were being considered to potentially address the problem of nausea following chemotherapy.

Indeed, contemporary literature suggested exploring "new anti-emetics with other mechanisms of action" for treating patients whose nausea was not under control. (*See, e.g.*, Ex. 1010 at 143.) As Dr. Peroutka agreed at his deposition, in 2009, there would have been scientific interest in looking for drugs with new mechanisms of action for patients suffering from nausea after chemotherapy. (Ex. 2086 at 60:10-61:22, 100:16-23, 101:21-102:1.) Below, I discuss some exemplary compounds that were considered promising candidates at that time.

1. Olanzapine

74. Olanzapine is an FDA-approved antipsychotic that received approval for schizophrenia in 1996. (Ex. 2098 at 1.) The chemical structure of the olanzapine compound is below:



(Ex. 2098 at 24.) Olanzapine blocks multiple receptors including "dopamine at D_1, D_2, D_3 and D_4 brain receptors, serotonin at 5-HT_{2a}, 5-HT_{2c}, 5-HT_3 and 5-HT_6

receptors, catecholamines at α_1-adrenergic receptors, acetylcholine at muscarinic receptors and histamine at H_1 receptors." (Ex. 2036 at 524.)

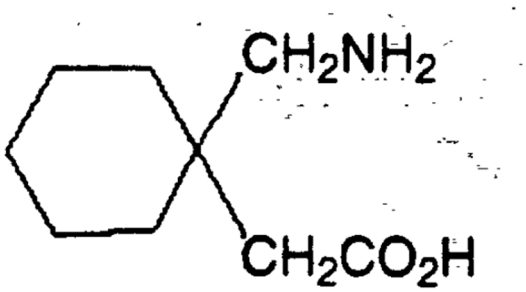
75. In November 2009, a POSA would have understood that olanzapine in combination with a 5-HT_3 receptor antagonist and dexamethasone "***showed promise in controlling acute and delayed nausea*** in patients receiving moderately and highly emetogenic chemotherapy." (Ex. 2036 at 528 (emphasis added); *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-HT_3-receptor antagonist and a corticosteroid."); Ex. 2037 at 588 ("studies have also shown the value of olanzapine for delayed and refractory emesis and nausea").) In my opinion, and as Dr. Peroutka likewise testified at his deposition, a POSA at the relevant time could have believed that olanzapine could help patients suffering from nausea. (*See* Ex. 2086 at 132:4-18, 134:1-16.)

76. Subsequent research after 2009, including human clinical studies, confirmed that olanzapine could potentially allow for the control of nausea as part of a treatment for CINV. Specifically, studies showed that, when added as a fourth component 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 and published in the *New England Journal of Medicine*, investigators compared the combination of olanzapine plus triple therapy (*i.e.*, olanzapine plus dexamethasone, 5-HT_3 receptor antagonist, and aprepitant) (*i.e.*, "quadruple therapy") to triple therapy alone. (Ex. 2039 at 134.) Investigators 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

77. Gabapentin is an FDA-approved antiepileptic drug approved for the prevention and control of partial seizures (convulsions) in the treatment of epilepsy. (Ex. 2099 at 13.) The structure of the gabapentin is below:



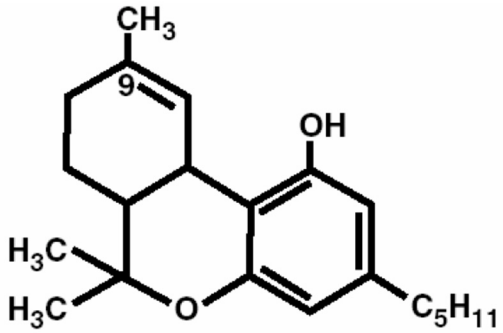
(Ex. 2099 at 1.)

78. By November 2009, a study with patients receiving HEC for breast cancer "suggested that the anti-epileptic gabapentin may reduce delayed nausea," but also 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.) A POSA at that time would have had access to this study and could have explored gabapentin as a possible treatment for delayed nausea after chemotherapy. I note that Dr. Peroutka also agrees that gabapentin is another agent that a POSA could have considered for modifying existing triple therapy to control nausea. (Ex. 2086 at 134:23-135:4.)

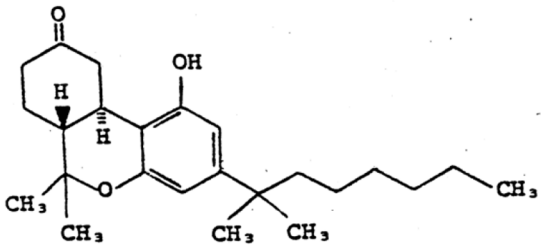
3. Cannabinoids

79. Cannabinoids are a class of biological compounds that bind to cannabinoid receptors. Cannabinoids are sourced from plants within the cannabis genus (*e.g.*, marijuana plants).

80. By November 2009, two oral formulations of cannabinoids (dronabinol and nabilone) had been approved by the FDA for use in patients suffering from CINV. (Ex. 2036 at 525; Ex. 2042; Ex. 2043.)



Dronabinol (Ex. 2042 at 1)



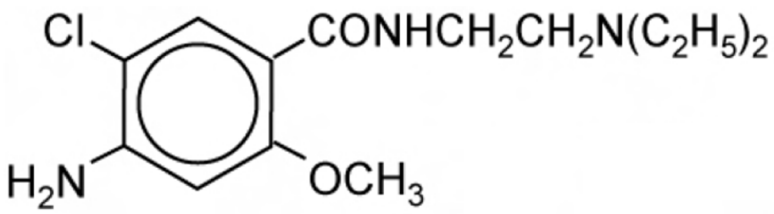
Nabilone (Ex. 2043 at 1)

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 they may have a role in controlling emesis and/or nausea. (Ex. 2036 at 525; Ex. 2037 at 578, 589-90.) In 2009, a POSA would have thought that cannabinoids may be useful in the control of chemotherapy-induced nausea based on their unique mechanism of action. (Ex. 2036 at 528; Ex. 2001 at 1872, 1872 (Table XII), 1874 ("cannabinoids may be useful in chemotherapy-induced nausea").) I note that Dr. Peroutka also

agrees that cannabinoids are another potential drug class a POSA could consider for modifying existing triple therapy to control nausea. (Ex. 2086 at 136:15-21.)

4. Metoclopramide

81. Metoclopramide is an FDA-approved dopamine/5-HT_3 receptor antagonist indicated for short term-therapy for adults with symptomatic, documented gastroesophageal reflux who fail to respond to conventional therapy. (*See, e.g.*, Ex. 2036 at 519 (Table III); Ex. 2097.)



(Ex. 2097 at 2.)

82. A POSA in 2009 would understand that metoclopramide, when used at high doses, is an effective antiemetic when combined with dexamethasone and lorazepam. (Ex. 2082 at 759; Ex. 2001 at 1872 (Table XII); Ex. 2036 at 519 (Table III).)

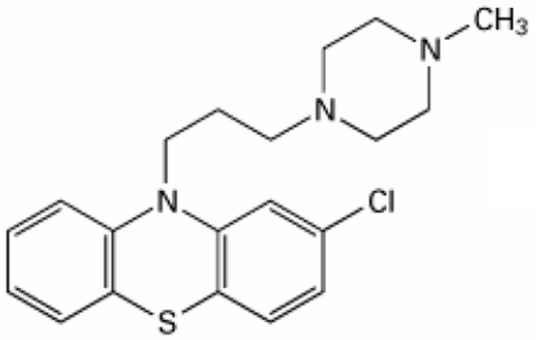
83. As of 2009, the NCCN Guidelines included metoclopramide as a choice for physicians to prescribe to patients receiving low-emetogenic chemotherapy. (Ex. 2037 at 577.) Further, metoclopramide was also listed as a

choice for physicians to prescribe to patients who experienced breakthrough nausea or emesis, regardless of the chemotherapy being administered. (Ex. 2037 at 578.)

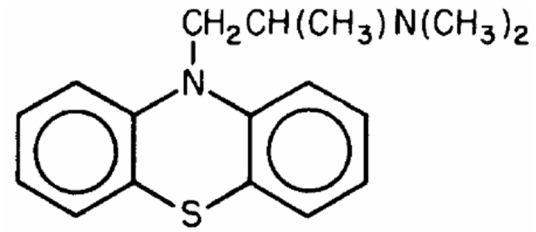
5. Phenothiazines (Prochlorperazine/Promethazine)

84. Phenothiazines are a class of drugs that were commonly used as antiemetics prior to the approval of 5-HT_3 receptor antagonists. (*See, e.g.*, Ex. 2001 at 1872, 1872 (Table XII); Ex. 2036 at 519 (Table III).) This class of drugs are dopamine receptor antagonists, meaning they engage with dopamine receptors that are known to exist in the chemoreceptor trigger zone. (Ex. 2036 at 518.)

85. Examples of phenothiazines include prochlorperazine and promethazine, both of which have been FDA-approved. (*See, e.g.*, Ex. 2037 at 578; Ex. 2093; Ex. 2094.)



Prochlorperazine (Ex. 2093 at 1)



Promethazine (Ex. 2094 at 1)

Prochlorperazine is indicated for the control of "severe nausea and vomiting," and acts as a dopamine receptor antagonist depressing the chemoreceptor trigger zone. (*See, e.g.*, Ex. 2093 at 2; Ex. 2036 at 518.) Promethazine is indicated for

"prevention and control of nausea and vomiting associated with certain types of anesthesia and surgery," "[a]ctive and prophylactic treatment for motion sickness," and [a]ntiemetic therapy in postoperative patients." (Ex. 2094 at 2 (Phenergan Label).)

86. As of November 2009, the NCCN Guidelines included both prochlorperazine and promethazine as an option for antiemesis. (Ex. 2037 at 577-78.) In particular, prochlorperazine was listed as a choice for physicians to prescribe to patients receiving low-emetogenic chemotherapy. (Ex. 2037 at 577.) Furthermore, prochlorperazine and promethazine were also listed as a potential choice for physicians to prescribe to patients who experienced breakthrough nausea or emesis, regardless of the chemotherapy emetogenic class being administered. (Ex. 2037 at 578.) In November 2009, a POSA could have explored adding phenothiazines, like prochlorperazine and promethazine, to triple therapy for better control of nausea, as their addition would provide a different mechanism of action (*i.e.*, dopamine receptor antagonism) to the existing drug classes that were used in triple therapy.

VI. ANALYSIS OF CERTAIN LITERATURE CITED DR. PEROUTKA

A. Prior Art Shows Aprepitant Was Not Effective Against Nausea, and NK-1 Receptor Antagonists Were Unlikely to Treat Nausea

87. In his declaration, Dr. Peroutka opines that "experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea." (Ex. 1009 at ¶ 1332.) Dr. Peroutka bases his opinion that "[a]prepitant was known to provide anti-nausea therapeutic effect during the acute period following administration of highly emetogenic chemotherapy," (Ex. 1009 at ¶ 1352), primarily on the 2008 Emend® (aprepitant) Label (Ex. 1030)[12] and the Campos publication (Ex. 1023). (Ex. 1009 at ¶¶ 1330-59.) By way of background, Emend® is the brand name for oral aprepitant tablets approved by the FDA in 2003 and marketed by Merck. (Ex. 2002.) Campos is a reference that was published by Merck scientists in 2001, prior to the Emend® Label. (Ex. 1009 at ¶¶ 1352-54.) I disagree with Dr. Peroutka's opinions.

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

88. In November 2009, a POSA would have understood that triple therapy consisting of dexamethasone, a 5-HT_3 receptor antagonist, and aprepitant was effective in controlling chemotherapy-induced vomiting, but was not effective in controlling chemotherapy-induced nausea. As I explain below, the aprepitant-based triple therapy references that Dr. Peroutka relies on do not show that aprepitant was effective in controlling chemotherapy-induced nausea. In particular, the Emend® Label shows that aprepitant did not achieve a statistically significant[13] reduction in either nausea or significant nausea following chemotherapy, as compared to standard therapy. In addition, a POSA in November 2009 would have known that the clinical studies that followed Campos concluded that "[t]he control of nausea in patients receiving MEC or HEC remains a significant problem. The role of the 3-day aprepitant regimen in the prevention of nausea is unclear, with data from phase III studies being inconsistent." (Ex. 2001

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[13] The p-values for "no nausea" and "no significant nausea" in the Emend® Label, as well as in the major aprepitant Phase III clinical studies, were greater than 0.05, meaning a POSA would not be able to determine whether any observed effect could be attributed to chance.

at 1874.) This fact is confirmed by other industry publications, including ones cited by Dr. Peroutka.

89. Dr. Peroutka cites numerous publications regarding aprepitant and its role in triple therapy. I provide my thoughts on these publications below and explain why triple therapy did not control nausea compared to standard therapy.

1. Herrstedt (Ex. 1010)

90. Herrstedt is a review article that summarizes the development of antiemetic therapy with a "focus on the importance of two new classes of antiemetics: 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 antiemetics has led to a significant decrease in a number of patients suffering from chemotherapy-induced ***vomiting***." (Ex. 1010 at 143 (emphasis added).)

91. Herrstedt states that "[t]he first nonpeptide 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 a "large number of NK_1-receptor antagonists have been investigated, but only aprepitant has been marketed, and only one other, casopitant, is so far in phase III." (Ex. 1010 at 146.)

92. 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 serotonin$_3$-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).)

93. Herrstedt notes that although the introduction of aprepitant and its use in the newly developed triple therapy (dexamethasone, a 5-HT$_3$ receptor antagonist, and aprepitant) had largely solved chemotherapy-induced vomiting (emesis), triple therapy did not control nausea. (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.)

94. Herrstedt further notes 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 drugs such as gabapentin and olanzapine as having potential 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.) None of these suggestions included using an NK-1 receptor antagonist.

95. 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.)

2. The 2008 Emend® Label (Ex. 1030), the 2003 Emend® Label (Ex. 2016), and the Poli-Bigelli Reference (Ex. 1039)

96. As an initial matter, Dr. Peroutka and I agree that the 2008 Emend® Label (Ex. 1030), the 2003 Emend® Label (Ex. 2016), and the Poli-Bigelli reference (Ex. 1039) all discuss the same clinical trial data. (*See* Ex. 2086 at 167:22-168:07 ("Q. . . . Poli-Bigelli is referencing the study that's reported in Table 2 of the Emend IV label . . . A. Correct.").) Despite that, Dr. Peroutka provides separate but similar opinions for each reference. Regarding the 2008 Emend® Label (Ex. 1030) and the 2003 Emend® Label (Ex. 2016), Dr. Peroutka opines that "the Emend® Label… shows reduction of nausea (and in particular reducing significant nausea) for patients." (Ex. 1009 at ¶ 1334.) Regarding Poli-Bigelli (Ex. 1039), he opines that "Poli-Bigelli expressly confirms the antiemetic

dosing regimen treats of [sic] nausea and vomiting" following the administration of chemotherapy. (Ex. 1009 at ¶ 981.)

97. As I explain in detail below, I disagree with Dr. Peroutka's opinions regarding all three references for at least the following reasons. First, only the 2008 Emend® Label (Ex. 1030) provides a proper analysis of statistical significance because it was "adjusted for multiple comparisons," while the p-value calculations in the other two references were not. (*Compare* Ex. 1030 at Table 2, *with* Ex. 2016 at Table 2 and Ex. 1039 at Table 2.) Second, the 2008 Emend® Label calculated statistical significance for the nausea parameters (*i.e.*, p-values for "no nausea" and "no significant nausea") and expressly disclosed that aprepitant did not provide a statistically significant reduction of either nausea or significant nausea compared to placebo. Third, a POSA would have known that the statistical significance of "complete protection" was likely driven by its components of "no emetic episodes" and "no rescue therapy" because the "no significant nausea" component lacked statistical significance.

a. Each Reference Discusses the Same Clinical Trial Data

98. As Dr. Peroutka admitted during his deposition, Table 2 in the 2008 Emend® Label (Ex. 1030), Table 2 in the 2003 Emend® Label (Ex. 2016), and Table 2 in the Poli-Bigelli reference (Ex. 1039) all analyze the same clinical trial

data. (Ex. 2086 at 167:22-168:07 ("Q. … Poli-Bigelli is referencing the study that's reported in Table 2 of the Emend IV label… A. Correct."); *compare* Ex. 1030 at Table 2, *with* Ex. 2016 at Table 2 and Ex. 1039 at Table 2.) This fact is apparent when these tables are compared side-by-side across these three references:

2008 Emend® Label (Ex. 1030)

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
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

2003 Emend® Label (Ex. 2016)

Table 2

Percent of Patients Responding by Treatment Group and Phase for Study 2 — Cycle 1

ENDPOINTS	Aprepitant Regimen (N= 261)† %	Standard Therapy (N= 263)† %	p-Value
PRIMARY ENDPOINT			
Complete Response			
Overall‡	63	43	<0.001
OTHER PRESPECIFIED (SECONDARY AND EXPLORATORY) ENDPOINTS			
Complete Response			
Acute phase§	83	68	<0.001
Delayed phase‖	68	47	<0.001
Complete Protection			
Overall	56	41	<0.001
Acute phase	80	65	<0.001
Delayed phase	61	44	<0.001
No Emesis			
Overall	66	44	<0.001
Acute phase	84	69	<0.001
Delayed phase	72	48	<0.001
No Nausea			
Overall	49	39	0.021
Delayed phase	53	40	0.004
No Significant Nausea			
Overall	71	64	>0.050
Delayed phase	73	65	>0.050

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

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

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

Poli-Bigelli reference (Ex. 1039)

(Ex. 1030 at Table 2 (annotations added); Ex. 2016 at Table 2 (annotations added); Ex. 1039 at Table 2 (annotations added).)

99. In the annotated tables above, I used three blue boxes to indicate that each table compares the same aprepitant regimen group (261 patients) with the same standard therapy group (263 patients). Similarly, I used three red boxes to highlight that each table provides the same "no nausea" data for the overall phase (aprepitant = 49% and standard = 39%) and the delayed phase (aprepitant = 53% and standard = 40%). Likewise, I used three green boxes to highlight that each table provides the same "no significant nausea" data for the overall phase (aprepitant = 71% and standard = 64%) and the delayed phase (aprepitant = 73% and standard = 65%).

100. The only difference among these three tables is that the p-value calculations in the 2008 Emend® Label were corrected to adjust for multiple comparisons, and consequently found that the differences for "no nausea" are "[n]ot statistically significant when adjusted for multiple comparisons." (Ex. 1030 at Table 2; *see* Section VI.A.2.b.) Conversely, the 2003 Emend® Label and the Poli-Bigelli reference both provide the same, unadjusted p-values for "no nausea" in the overall phase ($P = 0.021$ or $P < 0.05$) and the delayed phase ($P = 0.004$ or $P < 0.01$) that were not yet adjusted for multiplicity. (Ex. 2016 at Table 2; Ex. 1039 at Table 2.) In fact, the 2003 Emend® Label expressly warns that "Table 2 includes

nominal p-values not adjusted for multiplicity." (Ex. 2016 at 5.) Failure to account for multiplicity when there are several endpoints evaluated in a study can increase the chance of false conclusions regarding the effects of the drug. (*See, e.g.*, Ex. 2073 at 1002 ("No multiplicity adjustments were made for the tolerability analysis; therefore, P values should be interpreted with caution."); Ex. 2076 at 22 ("Conventionally, the probability of Type I error is set at 5 percent or less or as dictated by any adjustments made necessary for multiplicity considerations.").) At his deposition, Dr. Peroutka even admitted that "the Bonferroni correction" accounts for multiplicity and is one of the major corrections that should, in general, be done. (Ex. 2086 at 170:18-172:1.) Similarly, he also admitted that Merck submitted, and the FDA approved, the 2008 Emend® Label with statistical significance removed because aprepitant did not show a statistically significant difference compared to standard therapy for "no nausea" (whether overall or delayed) when adjusted for multiple comparisons. (Ex. 2086 at 174:12-177:23.)

101. Therefore, in my opinion, a POSA in 2009 would have known that these three references were all discussing the same clinical trial data and would have credited the 2008 Emend® Label's updated p-values that were adjusted for multiplicity over the outdated nominal p-values that were provided in the two earlier references.

b. The 2008 Emend® Label Shows that Aprepitant Fails to Provide a Statistically Significant Effect Against Nausea

102. Dr. Peroutka opines that "the Emend label, in [his] opinion, shows reduction of nausea (and in particular reducing significant nausea) for patients," and that "statistical significance was not calculated for nausea parameters." (Ex. 1009 at ¶ 1334.) I disagree with Dr. Peroutka's opinion. In my opinion, the 2008 Emend® Label clearly calculated statistical significance for the nausea parameters (*i.e.*, "no nausea" and "no significant nausea") and expressly disclosed that those calculated p-values showed that, as compared to placebo, aprepitant did not provide a statistically significant reduction of either nausea or significant nausea. As I explain in detail below, a POSA would have understood the 2008 Emend® Label as showing that aprepitant plus a 5-HT_3 receptor antagonist and dexamethasone was no better at treating nausea than placebo plus a 5-HT_3 receptor antagonist and dexamethasone.

103. Table 1 below is copied directly from the text of the 2008 Emend® Label. This table shows that aprepitant's effect on nausea and significant nausea is ***not*** statistically significant for patients receiving HEC, as compared to standard therapy, and indicated by the "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.

(Ex. 1030 at 4-5 (annotations added).) In fact, Dr. Peroutka admitted during his deposition that in the pivotal study included as Table 1, aprepitant showed no statistically significant difference in the overall or and delayed phases for no nausea as compared to standard therapy. (*See* Ex. 2086 at 178:15-179:10, 179:18-180:2.) Instead, "[i]t show[ed] a numerical superiority, but not a statistical superiority." (Ex. 2086 at 179:8-10.) Dr. Peroutka likewise admitted during deposition that the study reported in Table 1 of the Emend® Label showed no statistically significant difference compared to standard therapy for both "no nausea" and "no significant nausea" in the overall and delayed phases. (Ex. 2086 at 179:18-181:3.)

104. In my opinion, a POSA would therefore have understood that, when statistical significance was calculated specifically for nausea parameters as endpoints, aprepitant failed to achieve statistical significance. Furthermore, a POSA would understand that a study would provide "convincing evidence of efficacy of the aprepitant regimen in the prevention of" nausea only if "the differences [were] statistically significant." (Ex. 1009 at ¶ 774 (citing Ex. 1037 at 4117); *see also* Ex. 2086 at 182:3-184:10, 194:21-196:22.) As a result, my opinion is that a POSA would have known that Table 1 does not disclose convincing evidence that the aprepitant regimen was effective in the reduction of either nausea or significant nausea.

105. As discussed above, Table 2 below is copied directly from the text of the 2008 Emend® Label. This table clearly shows that aprepitant's effect on nausea and significant nausea is ***not*** statistically significant for patients receiving HEC as compared to standard therapy, as indicated by either the "NS*" (green highlights) or the "NS**" (blue highlights) provided for the p-value:

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.

(Ex. 1030 at 5-6 (annotations added).) Notably, the difference for "no nausea" was found to be "[n]ot statistically significant when adjusted for multiple comparisons." (*Id*. (green highlights).) Dr. Peroutka admitted during his deposition that when looking at Table 2, it is "statistically accurate" to say "that aprepitant did not show a statistically significant difference compared to standard therapy for no nausea, whether it's overall or delayed." (Ex. 2086 at 176:12-24.) Dr. Peroutka likewise admitted during his deposition that when looking at Table 2, aprepitant did not show a statistically significant difference compared to standard therapy for the overall and delayed phases of no significant nausea, rather "[i]t only showed a numerical superiority, not statistical." (Ex. 2086 at 177:4-13.) Again, a POSA

would not rely on a numerical difference (rather than statistical significance) as convincing evidence of aprepitant's efficacy in reducing nausea.

106. Similarly, Table 3 below is copied directly from the text of the 2008 Emend® Label and shows that aprepitant's effect on "no nausea" and "no significant nausea" is ***not statistically significant*** for patients receiving MEC as compared to standard therapy, and as indicated by the "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.

(Ex. 1030 at 7-8 (annotations added).)

107. Accordingly, a POSA would have understood these provisions of the 2008 Emend® Label as demonstrating that the aprepitant regimen has no

statistically significant effect against nausea or significant nausea as compared to standard therapy.

108. In addition, a POSA's understanding of the 2008 Emend® Label would have been confirmed by other publications at the relevant time, which taught, for example, that "[a]ccording to its package insert, aprepitant 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 (citing Ex. 1030).) Similarly, a POSA's understanding of the 2008 Emend® Label would have been aligned with what the art in November 2009 taught as a whole because many references and clinical trials expressly stated that aprepitant did not achieve a statistically significant reduction in either nausea or significant nausea as compared to standard therapy. (*See, e.g.*, Section VI.A; Ex. 2036 at 522, ("The control of nausea was not improved with the use of aprepitant."), 527 ("Aprepitant did not improve nausea in the study."), 529 ("Although aprepitant has been highly effective in controlling emesis, it has not been effective in controlling nausea."); Ex. 1034 at 2828-29 ("There was no significant effect of aprepitant on nausea . . . ."); Ex. 1048 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, 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."); Ex. 2073 at 1005 ("Nausea occurred in fewer patients in the aprepitant group, but the results were not significantly different from those in the control group. This result is in line with other aprepitant studies in which patients received either highly or moderately emetogenic chemotherapy, which suggests that the neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting.") (citing Ex. 1034 and Ex. 1037).)

109. Indeed, as I discuss below in the sections directed to Herrington, Warr, Hesketh, and Yeo, many of the references that Dr. Peroutka specifically relies on to allegedly support his opinions would have taught a POSA that aprepitant is ***not*** effective at controlling nausea. (*See, e.g.*, Sections VI.A.4-6, 8; Ex. 1009 at ¶¶ 74, 118-22, 1347, 1368, 1390.)

110. Consequently, Dr. Peroutka's opinions that the data in the Emend® Label "shows reduction of nausea (and in particular reducing significant nausea) for patients" and "statistical significance was not calculated for nausea parameters," are incorrect. (Ex. 1009 at ¶ 1334.) To the contrary, the Emend® Label shows that statistical significance was calculated for the nausea parameters,

and that aprepitant's addition to standard therapy failed to provide a statistically significant reduction in nausea or significant nausea for patients.

c. Dr. Peroutka Improperly Relies on Composite Endpoints

111. In his declaration, Dr. Peroutka states that "when evaluating whether a patient achieved 'complete protection,' the Emend® Label requires (1) no emetic episodes; (2) no rescue therapy; and (3) no significant nausea." (Ex. 1009 at ¶ 1334 (citing Ex. 1030).) He then opines that "a POSA would have understood this ['complete protection'] data to illustrate an improvement in the patients receiving aprepitant, including a decrease of significant nausea." (Ex. 1009 at ¶ 1336.) Dr. Peroutka also makes a similar argument regarding Figure 3 of the Emend® Label, which combines no emesis and no significant nausea in a single metric. (Ex. 1009 at ¶ 1338.)

112. I disagree with the interpretation of the data in the Emend® Label that Dr. Peroutka offers for his opinions. Separate consideration of specific efficacy and safety outcomes as additional primary variables is important. (Ex. 2076 at 8; Ex. 2085 at 14-15.) Yet, Dr. Peroutka ignores that the specific efficacy results for "no nausea" and "no significant nausea" in that label already show a lack of statistical significance as compared to standard therapy. A problem with composite endpoints is that their use could (in some cases) lead to two products being

declared equivalent in treating a given condition, despite having very different profiles of beneficial and adverse effects. Treatment differences between patient groups could render the composite endpoint of "complete protection" misleading and could lead to the inaccurate conclusion that all the components contribute equally to that difference, when in reality only one component could be the driving force.

113. In fact, during his deposition, he admitted that he cannot "evaluate whether or not the no emesis difference skewed the data in a way to show a statistically significant difference for complete protection . . . because those data are not available." (Ex. 2086 at 200:8-19.) Dr. Peroutka also admitted that he does "not know that any of the other composite endpoints are why we're seeing a statistically significant difference for complete protection, as opposed to that being done because of no nausea." (Ex. 2086 at 200:21-201:21; *see also id.* at 202:21-203:14.) This admission underscores exactly why a POSA would not rely on the composite endpoint of complete protection to assess whether aprepitant-based triple therapy would have a statistically significant impact on nausea as compared to standard therapy.

114. In addition, 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. ***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 that would lead a POSA to conclude this result was clinically meaningful or to change his or her clinical practice. (*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" following chemotherapy.

115. ***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.) As I discussed above in Section V.B.1, the "complete protection" value is a "composite"

endpoint.[14] (*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 emetic episodes," (2) "no use of rescue therapy," and (3) "no significant nausea (maximum VAS <25 mm on a 0 to 100 mm scale)." (*See* Ex. 1030 at 4.) In my opinion, a POSA would not interpret a difference in "complete protection" as equivalent to a statistically significant difference in "no significant nausea." (*See* Ex. 1030 at 4-5, 7-8.) Moreover, when specifically evaluating a drug for potential control of nausea, a POSA reading the Emend® Label would recognize and focus primarily on the label's express data on "no significant nausea," rather than focus on a composite endpoint.

116. Due to the very nature of a composite endpoint, "complete protection" cannot be used to prove a statistically significant effect on its nausea component alone. In fact, the FDA noted the observed treatment difference for "complete response" in Table 3 of the Emend® Label was primarily driven by the no-emesis

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[14] If objective variables (*e.g.*, no emesis or no rescue therapy) are considered by the investigator when using a composite endpoint (*e.g.*, complete protection or complete response), then those objective variables should be considered as additional primary or, at least, important secondary variables.

component. (Ex. 1030 at 8 ("The difference between treatment groups was primarily driven by the "No Emesis Endpoint," a principal component of this composite primary endpoint.").) Similarly, Table 3 also assessed "the impact of nausea and vomiting on patients' daily lives … using the FLIE," and found the "difference between treatment groups was primarily driven by the 'No Vomiting Domain' of this composite endpoint." (Ex. 1030 at 8.) Accordingly, a significant composite result for "complete protection" can occur even when "no nausea" is not independently statistically significant.

117. Indeed, both the "no emesis" and "no use of rescue antiemetics" endpoints, which measure aprepitant's impact on vomiting and do not include nausea (*see* Ex. 1010 at 148), were statistically significant. (*See* Ex. 1030 at 4-5, 7-8.) Thus, data suggest 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, rather than the "no significant nausea" component. (*See* Ex. 1030 at 4-5, 7-8.)

d. Dr. Peroutka's Reliance on Poli-Bigelli, Separate from the Emend Label, Is Improper

118. Dr. Peroutka opines that "Poli-Bigelli expressly confirms the antiemetic dosing regimen treats of [sic] nausea and vomiting in response to emetogenic chemotherapy during both the acute phase and the delayed phase."

(Ex. 1009 at ¶ 981.) He also opines that "Poli-Bigelli suggests the therapeutic regimen is effective to prevent and reduce the severity of nausea following the administration of chemotherapy." (Ex. 1009 at ¶ 1290.) I disagree. As I explained in the previous sections, the 2008 Emend Label corrected the p-value calculations of the study discussed in Poli-Bigelli to account for multiplicity. Using the multiple comparisons correction (also known as the "Bonferroni correction") is important to conservatively protect against false positives when multiple statistical tests are conducted simultaneously. Therefore, a POSA would have recognized that the Poli-Bigelli reference reflects a less accurate analysis of the same data, as shown by Table 2, which shows "no nausea" in the overall and delayed phases with p-values less than 0.05 and 0.01, respectively. (*See, e.g.*, Ex. 1009 at ¶ 981.) In my opinion, a POSA would recognize that the Poli-Bigelli disclosure presents a false positive for no nausea, as the p-value was not statistically significant after adjustment for multiple comparisons. Accordingly, a POSA would no longer consider Poli-Bigelli a reliable source of information on aprepitant or aprepitant-based triple therapy.

3. Campos (Ex. 1023)

119. Dr. Peroutka opines that "Campos discloses aprepitant's beneficial effect for nausea and shows it provided significant additive benefit during the acute phase of CINV." (Ex. 1009 at ¶ 1353.) I disagree, however, because a POSA in

2009 would have viewed the Campos study as an outdated 2001 publication that had been superseded, at the very least, by the Emend® Label. In addition, a POSA would have recognized that the findings reported by Campos were unreliable due to the nominal p values, extreme dosing regimen, and improbable data sets.

a. Campos Was Outdated and Superseded by Merck

120. Campos was written by Merck scientists who were working with aprepitant at that time. After Campos was published in 2001, these same scientists continued to study aprepitant, eventually obtaining a much better understanding of its properties. (Ex. 1023 at 1759.) And in subsequent clinical trials – such as the two pivotal studies included in the Emend Label – the Merck scientists determined that aprepitant did not provide a statistically significant reduction in nausea or significant nausea for patients. (*See, e.g.*, Ex. 1030 at 4-5.) In fact, Merck's various publications discussing its subsequent clinical trials expressly acknowledge that aprepitant lacked clinical efficacy against nausea or significant nausea.

121. By way of example, the Hesketh reference (which I discuss in further detail below in Section VI.A.6) was published on November 15, 2003, and disclosed that "[t]his study was funded by Merck Research Laboratories." (Ex. 1037 at 4112, 4118.) Furthermore, Alexandra D. Carides is a named author of both the Hesketh and Campos references. (*Compare* Ex. 1037 at 4112, *with* Ex. 1023 at 1759.) Importantly, Hesketh discusses Merck's "multicenter, randomized,

double-blind, placebo-controlled phase III study [that] was performed to establish definitively the superiority of the aprepitant regimen versus standard therapy in the prevention of chemotherapy-induced nausea and vomiting." (Ex. 1037 at 4112.) Hesketh taught a POSA that "[i]n the comparisons for total control, no nausea, and no significant nausea, results for the aprepitant regimen were consistently numerically higher, though the differences did not reach statistical significance." (Ex. 1037 at 4115.)

122. Another example is the Warr reference (which I discuss in further detail below in Section VI.A.5), which was published on April 20, 2005, "[s]upported by Merck & Co Inc.," and authored by Merck employees and consultants. (Ex. 1034 at 2822, 2829.) Paul J. Hesketh, Steven M. Grunberg, Richard J. Gralla, and David G. Warr are named authors of both the Hesketh and Warr references. (*Compare* Ex. 1037 at 4112, *with* Ex. 1034 at 2822.) Notably, Warr taught a POSA that "[t]here was no significant effect of aprepitant on nausea," and "[t]he more pronounced effect of aprepitant and 5-HT_3-receptor antagonists on the prevention of vomiting compared with nausea implies that serotonin and substance P may play a relatively more important role in the pathogenesis of vomiting than of nausea, and that other neurotransmitters may also be involved in the pathogenesis of these symptoms, especially nausea." (Ex. 1034 at 2828-29.)

123. Accordingly, a POSA would have recognized that Campos is an outlier and would not have relied upon it, because Merck itself later stated that aprepitant does not provide a significant effect against nausea. (*See, e.g.*, Ex. 1037 at 4115; Ex. 1034 at 2828-29.) Indeed, a POSA would have also recognized that the prior art as a whole confirms that Campos is an outlier, given that its results were inconsistent with other studies (Section VI.A.4-8) that evaluated whether aprepitant could reduce nausea to a statistically significant degree. (*See, e.g.*, Ex. 2036 at 522, 527, 529; Ex. 1048 at 531-34; Ex. 2037 at 587; Ex. 2073 at 1005.) I am not aware of any subsequent aprepitant study results that are consistent with Campos, and Dr. Peroutka has not cited any such results. (*See* Ex. 2086 at 230:9-231:6 (Dr. Peroutka admitting that Campos is the only study he has identified as showing a statistically significant difference in the prior art for an aprepitant regimen treating nausea or significant nausea).)

124. In other words, a POSA would have recognized that there was no independent substantiation of Campos's experimental results demonstrating consistency across multiple studies, which greatly increases the likelihood that a chance-driven, site-specific result led to Campos's erroneous conclusion that aprepitant is significantly effective against nausea. (*See* Ex. 2085 at 4-5.) Therefore, a POSA would have understood that, in deciding whether to rely on the single trial in Campos, it was critical to consider the possibility of an erroneous

result and to examine all available data for their potential to support or undermine reliance on Campos alone.

b. The Findings of Campos Were Unreliable

125. In my opinion, a POSA would not have relied on the data provided by Campos in the absence of independent substantial evidence for various other reasons as well. First, Campos specifies that "no or minimal nausea [was] defined **post hoc** as a visual analog scale rating that averaged less than 5 mm over the entire time interval," and only "**[n]ominal P values are reported**." (Ex. 1023 at 1761 (emphasis added).) As I discussed earlier, nominal p-values are not adjusted for multiplicity, which reduces the likelihood of false positives, ensuring more reliable results. Second, Campos reports median visual analog scale (VAS) nausea scores of 7 mm or less on days 1 to 5 across all treatment groups. (Ex. 1023 at 1764, Table 4.) In other words, Campos improbably reported that 100% of its patients, regardless of regimen, experienced no significant nausea (*i.e.*, nausea VAS of <25mm) for the overall period. (Ex. 1023 at 1764, Table 4.) This finding is highly atypical based on both the rates of no significant nausea reported by prior art trials and my own clinical experience. Another factor adding to Campos's unreliability is that "[a]dditional medication was available to treat emesis or nausea at any time." (Ex. 1023 at 1759.)

126. Furthermore, in my opinion, a POSA would have also known that the Campos study is unreliable because Campos used an aprepitant dosing regimen that is ~5.5 times higher than the FDA-approved Emend® dosing.[15] For instance, Dr. Peroutka specifically relies on Group II, which received 10 µg/kg of granisetron intravenously, 20 mg of dexamethasone orally, and 400 mg of aprepitant orally on day 1, followed by 300 mg of aprepitant orally on days 2 to 5. (Ex. 1009 at ¶ 1353; Ex. 1023 at 1759-60.) In the table below, I compare the regimens of Campos, Grunberg, and Emend® Label to demonstrate how disparate the amount of aprepitant administered over five days in Campos is compared to both Grunberg and the Emend® Label:

[15] The dosing in Campos is also inconsistent with the aprepitant dosing in the NCCN guidelines. (Ex. 2037 at 575.)

Aprepitant Triple Therapy Dosing Regimens				
Source		**Campos**	**Grunberg**	**Emend® Label**
Day 1	**Aprepitant**	400 mg orally	285 mg orally	125 mg orally
	5-HT_3 Receptor Antagonist	10 µg/kg granisetron IV	0.25 mg palonsetron IV	32 mg ondansetron IV
	Dexamethasone	20 mg orally	20 mg orally	12 mg orally
Day 2 & Day 3	**Aprepitant**	300 mg orally	N/A	80 mg orally
	Dexamethasone	≤16 mg orally as needed	As needed	8 mg orally
Day 4	**Aprepitant**	300 mg orally	N/A	N/A
	Dexamethasone	≤16 mg orally as needed	As needed	8 mg orally
Day 5	**Aprepitant**	300 mg orally	N/A	N/A
	Dexamethasone	≤16 mg orally as needed	As needed	N/A
Total Day 1-5	**Aprepitant**	1600 mg	285 mg	285 mg
	Dexamethasone	20–84 mg	20 mg (?)	28 mg

127. I note that Dr. Peroutka opines that the Grunberg study is not comparable to the '357 patent's studies because, for example, "Grunberg did not administer the FDA-approved dose of aprepitant on Day 1 (125 mg)." (Ex. 1009 at ¶¶ 1374-76.) At the same time, Dr. Peroutka opines that "a single dose of aprepitant 285 mg . . . might affect nausea and vomiting, such as whether adverse events (including nausea and vomiting) could arise." (Ex. 1009 at ¶ 1376.) But when opining that Campos is a comparable study that "discloses aprepitant's beneficial therapeutic effect for nausea and shows it provided significant additive benefit during the acute phase of CINV," Dr. Peroutka ignores the fact that Campos did not administer the FDA-approved dose of aprepitant. (Ex. 1009 at ¶ 1353.) Moreover, Campos administered 1600 mg of aprepitant over five days compared to the 285 mg of aprepitant administered by both Grunberg and the FDA-approved Emend® Label.

4. Herrington (Ex. 1016)

128. In my opinion, Herrington would have taught a POSA that "[t]he combination of palonosetron and aprepitant is safe and effective in the prevention of ***chemotherapy-induced emesis (CIE)***," but not chemotherapy-induced nausea. (Ex. 1016 at 2080 (emphasis added).) Herrington also discloses that "[a]prepitant is a substance P/neurokinin-1 (NK1)-receptor antagonist approved for use in

combination with a 5-HT3–receptor antagonist and dexamethasone for ***acute and delayed CIE prevention***." (Ex. 1016 at 2080 (emphasis added).)

129. The Herrington study consisted of three regimens, referred to as Arms A, B, and C:

Herrington Dosing Regimens			
Day	**Arm A**	**Arm B**	**Arm C**
Day 1	Aprepitant 125 mg orally	Aprepitant 125 mg orally	Placebo
	Palonosetron 0.25 mg IV	Palonosetron 0.25 mg IV	Palonosetron 0.25 mg IV
	Dexamethasone 12 mg orally	Dexamethasone 12 mg orally	Dexamethasone 18 mg orally
Days 2 and 3	Aprepitant 80 mg orally	Placebo	Placebo
	Dexamethasone 8 mg orally	Dexamethasone 8 mg orally	Dexamethasone 8 mg orally
Day 4	Dexamethasone 8 mg orally	Dexamethasone 8 mg orally	Dexamethasone 8 mg orally

(Ex. 1016 at 2081 ("On Day 1, Arms A and B received a single dose of palonosetron 0.25 mg intravenously and dexamethasone 12 mg orally before receiving highly emetogenic chemotherapy. In Arm A, patients received the FDA-approved 3-day regimen of aprepitant 125 mg orally on Day 1, followed by 80 mg orally per day on Days 2 and 3. Patients in Arm B received aprepitant 125 mg orally on Day 1, followed by a matching placebo on Days 2 and 3. Arm C

involved palonosetron 0.25 mg intravenously and dexamethasone 18 mg orally on Day 1. Dexamethasone and aprepitant were encapsulated to maintain blinding across the 3 arms. On Days 1-3, a placebo resembling aprepitant was administered. All patients in the 3 study arms received dexamethasone 8 mg orally daily on Days 2–4, and all received palonosetron 30 minutes before chemotherapy and aprepitant or placebo 60 minutes before chemotherapy.”).)

130. Herrington concluded that “[t]he ***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*** (Table 4 and Fig. 2).” (Ex. 1016 at 2084 (emphasis added).) Herrington further provides that “[t]he control of nausea was achieved in similar fashion between the 2 aprepitant arms. However, there was a trend toward better significant nausea prevention on Days 4-5 with the 3-day Arm A versus the single dose. In the 3-day arm, 88.5% versus 69.2% did not have significant nausea as defined by <25 mm on the visual analog scale (P = .09). It is unlikely that there is a true difference present because previously published data has not found a disparity. According to its package insert, aprepitant 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.)

131. Based on the disclosures regarding the aprepitant-based triple therapy regimen in Herrington, Herrington would have taught a POSA, that compared to

standard therapy consisting of palonosetron and dexamethasone, triple therapy consisting of dexamethasone, palonosetron, and aprepitant provides a statistically significant improvement in the prevention of chemotherapy-induced emesis (Ex. 1016 at 2080), but does not provide a statistically significant improvement in the reduction of nausea (Ex. 1016 at 2084, 2086). Despite relying on Herrington, Dr. Peroutka fails to address these express disclosures that directly contradict his opinion that "experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea." (Ex. 1009 at ¶¶ 1330-32.)

5. Warr (Ex. 1034)

132. Warr teaches "[s]everal large studies have shown that addition of aprepitant to a regimen including granisetron or ondansetron and dexamethasone improved the prevention of **emesis** throughout the acute and delayed phases in patients receiving cisplatin-based highly emetogenic chemotherapy (HEC)." (Ex. 1034 at 2823 (emphasis added).) The Warr study was designed to clarify the potential role of aprepitant in patients receiving MEC and compared the efficacy and tolerability of a three-day aprepitant regimen with a standard therapy control regimen, as summarized below:

Table 1. Study Medication Schedule

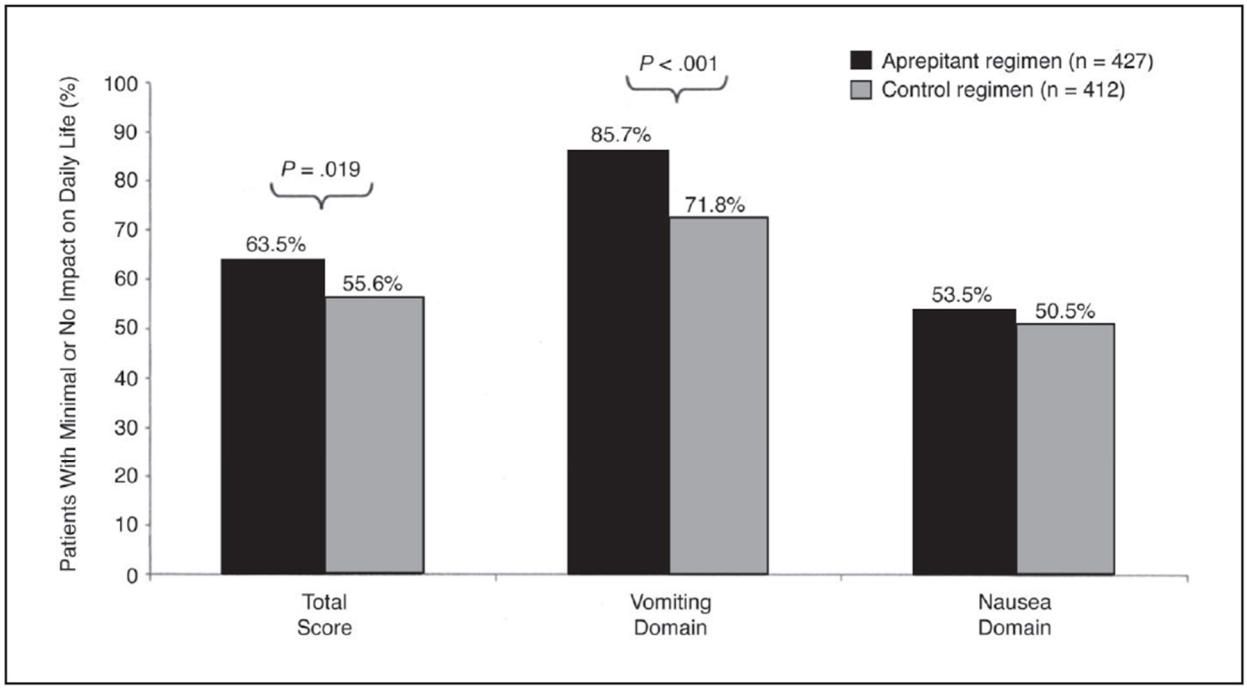
Regimen and Study Medication	Dose		
	Day 1	Day 2	Day 3
Aprepitant (n = 438)			
Aprepitant	125 mg po 1 hour before chemotherapy	80 mg po	80 mg po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	Placebo po bid	Placebo po bid
Dexamethasone	12 mg po 30 minutes before chemotherapy		
Control (n = 428)			
Aprepitant	Placebo po	Placebo po	Placebo po
Ondansetron	8 mg po 30 to 60 minutes before chemotherapy; 8 mg po 8 hours after first dose	8 mg po bid	8 mg po bid
Dexamethasone	20 mg po 30 minutes before chemotherapy		

Abbreviation: po, orally.

(Ex. 1034 at 2823-24.)

133. Warr discloses that "[o]n the FLIE questionnaire,[16] significantly more patients taking the aprepitant regimen reported minimal or no impact on daily living overall (Fig 4)." (Ex. 1034 at 2826.) Figure 4 is copied directly from the text and provided below:

[16] "The FLIE questionnaire is a validated patient-reported measure of the impact of CINV on daily life. It is a short, self-administered instrument containing two domains – one for nausea (9 items) and one for vomiting (9 items)." (Ex. 1034 at 2824.)



(Ex. 1034 at 2828.) Warr discloses that "[t]here were significant differences favoring aprepitant in the vomiting domain score (85.7% v 71.8%; P < .001), as well as in individual items, but not in the nausea domain score (53.5% v 50.5%)." (Ex. 1034 at 2826.) It also expressly discloses that "[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 (emphasis added).)

134. Warr concluded that "[i]n 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." (Ex. 1034 at 2828.) But unlike vomiting, "[t]here was no significant effect of aprepitant

on nausea." (Ex. 1034 at 2828-29.) Accordingly, Warr taught a POSA that "[t]he more pronounced effect of aprepitant and 5-HT_3-receptor antagonists on the prevention of vomiting compared with nausea implies that **serotonin and substance P may play a relatively more important role in the pathogenesis of vomiting than of nausea**, and that **other neurotransmitters may also be involved in the pathogenesis** of these symptoms, **especially nausea**." (Ex. 1034 at 2828-29 (emphasis added).)

135. Consequently, in my opinion, Warr would have taught a POSA that, compared to standard therapy consisting of ondansetron and dexamethasone, triple therapy consisting of aprepitant, ondansetron, and dexamethasone provides a statistically significant improvement in the prevention of chemotherapy-induced emesis (Ex. 1034 at 2828), but fails to provide a statistically significant improvement in the reduction of nausea (Ex. 1034 at 2827-29). Again, despite relying on Warr (*see* Ex. 1009 at ¶ 1368), Dr. Peroutka fails to address these express disclosures that directly contradict his opinion that "experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea." (Ex. 1009 at ¶¶ 1330-32.)

6. Hesketh (Ex. 1037)

136. The Hesketh study discloses that "[i]n early-phase clinical studies that included more than 1,200 cancer patients receiving their first cisplatin-based

chemotherapy, aprepitant demonstrated enhanced protection against acute emesis . . . when combined with dual therapy consisting of a 5-HT_3 RA and dexamethasone." (Ex. 1037 at 4113.) Hesketh further provides that "aprepitant significantly improved the prevention of delayed emesis" and thus "[t]his study was conducted to confirm these findings in a large phase III study." (Ex. 1037 at 4113.) The Hesketh study compared the efficacy and tolerability of a four-day aprepitant regimen with those of a standard therapy control regimen in patients receiving HEC. Each regimen is summarized below:

Hesketh Dosing Regimens		
Day	**Aprepitant**	**Control**
Day 1	Aprepitant 125 mg orally	Placebo
	Ondansetron 32 mg IV	Ondansetron 32 mg IV
	Dexamethasone 12 mg orally	Dexamethasone 20 mg orally
Days 2 and 3	Aprepitant 80 mg orally	Placebo
	Dexamethasone 8 mg orally	Dexamethasone 16 mg orally
Day 4	Dexamethasone 8 mg orally	Dexamethasone 16 mg orally

(Ex. 1037 at 4113 ("Patients in the standard therapy group received intravenous ondansetron 32 mg and oral dexamethasone 20 mg on day 1, followed by oral

dexamethasone 8 mg twice daily on days 2 to 4. Patients in the aprepitant group received oral aprepitant 125 mg plus intravenous ondansetron 32 mg and oral dexamethasone 12 mg on day 1, oral aprepitant 80 mg and oral dexamethasone 8 mg once daily on days 2 and 3, and oral dexamethasone 8 mg on day 4. Placebo capsules matching aprepitant, and placebo tablets matching dexamethasone were used to maintain blinding.”).)

137. Hesketh concluded that for complete response “[t]he aprepitant regimen was superior to standard therapy overall (days 1 to 5; 72.7% v 52.3%; P < .001), as well as in separate analyses of both the acute phase (89.2% v 78.1%; P < .001), and even more notably, the delayed phase (75.4% v 55.8%; P < .001).” (Ex. 1037 at 4115.) Similarly, “[t]he aprepitant regimen was also statistically superior in all comparisons for the secondary and exploratory end points of no emesis, no rescue therapy, and complete protection (Table 2).” (Ex. 1037 at 4115.) However, and most importantly, “[i]n comparisons for total control, **no nausea**, and **no significant nausea**, results for the aprepitant regimen were consistently numerically higher, though **the differences did not reach statistical significance** (**Table 2**).” (Ex. 1037 at 4115 (emphasis added).) Table 2 copied from the text with nausea parameters highlighted in yellow provided below:

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

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

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

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

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

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

§Analysis not planned.

(Ex. 1037 at 4116 (annotations added).) Hesketh concluded that "for the end points of no emesis, complete response, and complete protection . . . the differences were statistically significant," while "the groups [that] **did not differ statistically** [were] total control, **no nausea**, and **no significant nausea**." (Ex. 1037 at 4117 (emphasis added).)

138. In my opinion, Hesketh would have taught a POSA that that triple therapy consisting of aprepitant, ondansetron, and dexamethasone provides a statistically significant improvement compared to standard therapy of ondansetron and dexamethasone in the prevention of chemotherapy-induced emesis (Ex. 1037 at 4117), while the differences for "no nausea" and "no significant nausea" did not reach statistical significance, (Ex. 1037 at 4115). Again, despite relying on Hesketh (*see* Ex. 1009 at ¶ 1291), Dr. Peroutka fails to address these express

disclosures that directly contradict his opinion that "experimental data shows that a POSA would have understood aprepitant to be effective at treating nausea." (Ex. 1009 at ¶ 1332.)

7. Schmoll (Ex. 2073)

139. While Dr. Peroutka did not cite the Schmoll study, it was cited in Herrstedt – one of his primary references – as one of "[f]our phase III trials [that] have investigated the use of aprepitant." (Ex. 1010 at 146 (note 39).) In my opinion, the Schmoll study reaffirms the findings in both Warr (Ex. 1034) and Hesketh (Ex. 1037) that aprepitant "may have less impact on the nausea component of chemotherapy-induced nausea and vomiting." (Ex. 2073 at 1005 (citing [11] and [18], which are Hesketh and Warr, respectively).)

140. The Schmoll study "compared an aprepitant regimen with a control regimen of ondansetron + dexamethasone given for 4 days." (Ex. 2073 at 1000.) Schmoll was "the first study to compare the aprepitant regimen with a multiple-day ondansetron + dexamethasone regimen similar to that used in clinical practice in patients receiving their first cycle of cisplatin chemotherapy." (Ex. 2073 at 1001.) The Schmoll study compared the efficacy of a four-day aprepitant regimen in treating nausea and vomiting after chemotherapy with standard therapy in patients receiving HEC, and each regimen is summarized below:

Schmoll Dosing Regimens		
Day	**Aprepitant**	**Control**
Day 1	Aprepitant 125 mg orally	Placebo
	Ondansetron 32 mg IV	Ondansetron 32 mg IV
	Dexamethasone 12 mg orally	Dexamethasone 20 mg orally
Days 2 and 3	Aprepitant 80 mg orally	Placebo
	Placebo	Ondansetron 16 mg orally
	Dexamethasone 8 mg orally	Dexamethasone 16 mg orally
Day 4	Placebo	Ondansetron 16 mg orally
	Dexamethasone 8 mg orally	Dexamethasone 16 mg orally

(Ex. 2073 at 1001 ("In the aprepitant regimen, oral aprepitant was given on days 1-3 (day 1, 125 mg 1 h before cisplatin; days 2-3, 80 mg); ondansetron was given on day 1 only (day 1, 32 mg i.v. infused over 15 min at 30-60 min prior to cisplatin; days 2-4, oral placebo twice daily); and oral dexamethasone was given on days 1-4 (day 1, 12 mg 30 min before cisplatin; days 2-4, 8 mg in the morning and placebo in the evening). In the ondansetron + dexamethasone regimen, aprepitant placebo was given on days 1-3; ondansetron was given on days 1-4 (day 1, 32 mg

i.v. infused over 15 min at 30-60 min prior to cisplatin; days 2-4, 8 mg orally twice daily); and oral dexamethasone was given on days 1-4 (day 1, 20 mg 30 min before cisplatin; days 2-4, 8 mg twice daily).”).)

141. Based on its results, Schmoll concluded that “[n]ausea occurred in fewer patients in the aprepitant group, but the results were not significantly different from those in the control group.” (Ex. 2073 at 1005.) Table 2, copied from the text with nausea parameters highlighted in yellow, is provided below:

Table 2. Comparison of efficacy endpoints by treatment group

	Aprepitant regimen (N = 243) % of patients	Control regimen (N = 241) % of patients	Odds ratio	95% CI	P value for odds ratio[a]
Complete response[b]					
0–120 h	72.0	60.6	1.80	1.21–2.66	0.003
0–24 h	87.7	79.3	2.10	1.25–3.52	0.005
>24–120 h	74.1	63.1	1.78	1.20–2.65	0.004
No vomiting					
0–120 h	76.5	62.2	2.14	1.43–3.22	≤0.001
0–24 h	88.9	80.5	2.17	1.27–3.69	0.004
>24–120 h	79.0	64.3	2.24	1.48–3.40	≤0.001
No use of rescue therapy					
0–120 h	82.3	79.7	1.23	0.78–1.96	0.373
0–24 h	94.2	92.9	1.32	0.63–2.77	0.468
>24–120 h	83.5	81.7	1.17	0.73–1.88	0.517
No significant nausea[c]					
0–120 h	73.1	69.7	1.24	0.83–1.87	0.290
0–24 h	92.1	89.5	1.45	0.77–2.76	0.254
>24–120 h	75.9	72.1	1.28	0.84–1.94	0.248

[a]P value of logistic model including terms for treatment, gender, use of concomitant emetogenic chemotherapy and geographic region.
[b]Complete response = no vomiting and no use of rescue therapy.
[c]For No significant nausea, the Ns varied from 237 to 242. No significant nausea = score of <25 mm on 100-mm visual analog scale.

(Ex. 2073 at 1004.) This result, that the nausea occurring in the aprepitant group was not significantly different from that in the control group, was “**in line with other aprepitant studies** in which patients received either highly or moderately emetogenic chemotherapy, which **suggests that the neurokinin-1 receptor**

antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting." (Ex. 2073 at 1005 (emphasis added).)

142. Schmoll further disclosed that "[o]ther studies have also shown similar or slightly higher rates of nausea as an adverse event with the aprepitant regimen compared with control." (Ex. 2073 at 1005.) In my opinion, a POSA would have understood that the consistent lack of a statistically significant difference in "no nausea" and "no significant nausea" in Schmoll "suggests that the neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting." (Ex. 2073 at 1005).

8. Yeo (Ex. 1048)

143. The Yeo study "compare[d] the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of chemotherapy-induced nausea and vomiting (CINV) in patients who received moderately emetogenic chemotherapy." (Ex. 1048 at 529.) The aprepitant regimen was dosed over three days. Each regimen is summarized below:

Yeo Dosing Regimens		
Day	**Aprepitant**	**Control**
Day 1	Aprepitant 125 mg orally	Placebo
	Ondansetron 16 mg orally	Ondansetron 16 mg orally
	Dexamethasone 12 mg orally	Dexamethasone 20 mg orally
Days 2 and 3	Aprepitant 80 mg orally	Placebo
	Placebo	Ondansetron 16 mg orally
	Metoclopramide 20 mg as needed	Metoclopramide 20 mg as needed

(Ex. 1048 at 529 ("The aprepitant-based antiemetic regimen consisted of aprepitant 125 mg, ondansetron 8 mg, dexamethasone 12 mg, before chemotherapy and ondansetron 8 mg 8 h later on day 1; aprepitant 80 qd on days 2–3. The control arm of standard anti-emetic regimen consisted of ondansetron 8 mg and dexamethasone 20 mg before chemotherapy and ondansetron 8 mg 8 h later on day 1; ondansetron 8 mg bid on days 2–3. Patients in both study groups were given the same number of tablets to be taken, which consisted of aprepitant, ondansetron, dexamethasone and placebo. Patients were instructed to take rescue therapy (metoclopramide 20 mg every 6 h as required) if needed for nausea or vomiting.").)

144. The Yeo study explains that "[b]ased on the average nausea scores as measured using VAS, the standard deviation is around 19–20 and a 10 mm difference is generally considered clinically important. Assuming the response rate with control regimen is 40%, this study would have 80% power to detect 25% difference with two-sided alpha level at 0.05, the number of patients per group is 61 and the total number of patients to be recruited is 122." (Ex. 1048 at 531.) Yeo discloses that "there was no significant difference in the proportion of patients with reported complete response, complete protection, total control, 'no vomiting', 'no significant nausea' and 'no nausea.' The requirement of rescue medication appears to be lesser in the aprepitant group than the control group (11% vs. 20%; P = 0.06) (Table 2)." (Ex. 1048 at 532.) Table 2, copied from the text with nausea parameters highlighted in yellow, is provided below:

Table 2 Emesis endpoints in the overall time frame (0–120 h)

	Aprepitant-based (%)	Standard (%)	*P*-value
No vomiting	54.8	50.0	0.58
No rescue	82.3	67.7	0.06
No significant nausea	66.1	62.9	0.71
No nausea	30.6	35.5	0.57
Complete response	46.8	41.9	0.58
Complete protection	38.7	41.9	0.71
Total control	25.8	30.6	0.55

(Ex. 1048 at 532.)

145. Yeo likewise provided that "[w]hen the impact on daily living was assessed using the FLIE questionnaire, while there was no difference in the nausea domain and the total score between the two groups, patients on the standard regimen had a significantly worse quality of life in the vomiting domain assessment (mean score [SD] = 23.99 [30.80]) when compared with those on the aprepitant-based regimen (mean score [SD] = 3.40 [13.18]) (P = 0.0002) (Table 4)." (Ex. 1048 at 532.) Table 4, copied from the text with nausea data highlighted in yellow, is provided below:

Table 4 Patients' scoring for Functional Living Index Emesis questionnaire

	Aprepitant-based		Standard		*P*-value
	Mean score	SD	Mean score	SD	
Nausea domain	26.74	25.51	31.75	31.95	0.84
Vomiting domain	3.40	13.18	23.99	30.80	0.0002
Total score	11.24	15.66	23.12	30.49	0.45

(Ex. 1048 at 533.)

146. Yeo also reported that "[t]here was also no significant difference between the two groups with respect to all the parameters of emesis control in the acute and delayed time frames (Table 3)." (Ex. 1048 at 532.) Table 3, copied from the text with nausea parameters highlighted in yellow, is provided below:

Table 3 Emesis endpoints in the acute (0–24 h) and delay time frames (24–120 h)

	Acute (0–24 h)			Delay (24–120 h)		
	Aprepitant-based	Standard	*P*-value	Aprepitant-based	Standard	*P*-value
No vomiting	72.1	74.2	0.79	75.6	67.4	0.39
No rescue	98.4	95.2	0.31	83.6	71.2	0.10
No significant nausea	88.5	83.9	0.45	74.1	75.0	0.91
No nausea	62.3	59.7	0.76	47.3	59.5	0.29
Complete response	72.1	72.6	0.95	64.4	57.8	0.51
Complete protection	67.2	72.6	0.51	56.1	57.8	0.87
Total control	54.1	56.5	0.79	45.5	54.3	0.47

(Ex. 1048 at 533.)

147. Yeo explained that "the outcomes of the aprepitant-based treated patients were compared with those treated with the standard regimen, the latter group had a relatively higher proportion of patients taking rescue medication (18% vs. 32%), which has led to a similar proportion of patients achieving 'no vomiting' after chemotherapy. As 'no rescue medication' and 'no vomiting' were two components of 'complete response,' it could partly explain the equivocal rate of complete response in the two groups of patients." (Ex. 1048 at 533.) The study further explained that "when compared with a large international anti-emetic study which consisted of breast cancer patients mainly from the West, there appears to be ethnic differences in the willingness to take medications, with less Chinese patients taking rescue medication (18% vs. 41% in the aprepitant-based arms, and 32% vs. 44% in the standard arms). The Chinese are reluctant to take medications whenever these are considered to be 'not absolutely necessary.' As a consequence, the proportion of patients achieving 'no vomiting' status after chemotherapy was lower in the present study when compared with the international study (55% vs.

76% in the aprepitant-based arms, and 50% vs. 59% in the standard arms)." (Ex. 1048 at 533.)

148. Based on its results, Yeo concluded that "[a]lthough the efficacy of aprepitant-based anti-emetic regimen was similar to standard regimens, 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**. This confirms that the agent is active against vomiting induced by serotonin and substance P, **while nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy**." (Ex. 1048 at 534 (emphasis added).) In my opinion, Yeo would have taught a POSA that aprepitant-based triple therapy does not provide a statistically significant reduction in "no nausea" or "no significant nausea" as compared to standard therapy. Furthermore, Yeo would have taught a POSA substance P (and therefore NK-1 receptor antagonism) does not seem to play a significant role in the pathogenesis of nausea.

B. The Prior Art Provides Insufficient Data on NK-1 Receptor Antagonists as a Class and Netupitant in Particular

149. Dr. Peroutka opines that aprepitant was an approved compound from the NK-1 receptor antagonist drug class (Ex. 1009 at ¶ 845), and the NK-1 receptor antagonist drug class has an 80% success rate. (Ex. 2086 at 86:11-90:12, 269:14-

270:3.) However, the prior art and even the inventor of aprepitant himself make clear that aprepitant was not, in truth, just the first of many NK-1 receptor antagonists that were about to flood the market. Instead, aprepitant was the proverbial "one in a million" success story. For "[f]ollowing the discovery of the first non-peptide NK_1 receptor antagonist CP-96,345 in 1991," aprepitant was the ***only*** NK_1 receptor antagonist to obtain FDA approval even though "a remarkable number of small molecule NK1 receptor antagonists were identified by many pharmaceutical companies in the last decade." (Ex. 1011 at 1362.)

1. High Failure Rate of NK-1 Receptor Antagonists

150. Many NK-1 receptor antagonists were in development at the time of invention for a variety of different potential uses, but none of these uses were for the treatment of nausea following chemotherapy. In fact, NK-1 receptor antagonists had been investigated (mostly unsuccessfully) for a variety of different uses for a long time. "The first NK1-receptor antagonist was found in 1984 . . . [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.) Similarly, in 2007, the literature reported that "[a] large number of NK1-receptor antagonists have been investigated, but only aprepitant has been marketed, and only one other, casopitant, is so far in phase III." (Ex. 1010 at 146.) Indeed, by November 2009, a POSA would have known that GSK had abandoned

casopitant as a potential treatment for CINV, even after Phase III clinical trials had been completed and a new drug application had been filed with the FDA. (Ex. 2036 at 522.) As GSK announced in a press release in September 2009 (Ex. 2077; Ex. 1036), its decision was based on the company's assessment that significant further safety data would be required due to toxicity issues. (Ex. 1005 at 343, ¶ 27; *see also* Ex. 2077; Ex. 1036.) And even today, only three NK-1 receptor antagonists have been approved by the FDA as active pharmaceutical ingredients for treating CINV: aprepitant, netupitant, and rolapitant. The unpredictable nature of developing an NK-1 receptor antagonist treatment for CINV is evident in that high failure rate, which stands in stark contrast to the 80% success rate mentioned by Dr. Peroutka at his deposition.

151. In my opinion, the history underlying the development of aprepitant provides instructive context here. A 2004 publication by Dr. MacCoss, the scientist who led the discovery of aprepitant, highlighted the difficulty of developing new drugs. There, he specifically pointed to NK-1 receptor antagonists in stating that "it is very likely that tens of thousands of [NK-1 receptor antagonist] molecules have been prepared in the past decade as substance P antagonists, a large percentage of which likely exhibited sub-nanomolar potency at the NK-1 receptor, but only one has made it to market. This example highlights the difficulty and resources needed to optimize the ancillary properties of potent

inhibitors/antagonists so that they can become safe, viable medicines." (Ex. 2096 at 1812-13.) When developing drugs, "[o]ne must constantly be aware that the rapid synthesis of large numbers of molecules that are laden with ADME, physical property, or toxicological shortcomings may provide intriguing hits or leads, but they may not shorten the time to the elaboration of such a hit into a drug candidate." (Ex. 2096 at 1812.)

2. Hargreaves (Ex. 1012)

152. Hargreaves is a review article that sought to prove Merck's recently developed, radioactive, NK-1 receptor-specific tracer[17] was useful for (among other things) monitoring NK-1 receptor occupancy during *in vivo* positron emission tomography ("PET") studies. (*See* Ex. 1012 at 18-19; *see also id.* at 24 ("clinical studies suggest that [^{18}F]SPA-RQ represents a valuable tracer for PET imaging of NK_1 receptors in the CNS").) Hargreaves disclosed that the new tracer and its corresponding "methodology can be used to guide dosing in efficacy studies," (Ex.

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[17] Hargreaves disclosed "[t]he recent development of [^{18}F]SPA-RQ, a radio-active, brain-penetrant, nonpeptide tracer that binds to the NK1 receptor with high affinity and selectivity." (Ex. 1012 at 19.)

1012 at 19), "by providing important pharmacokinetic[18] and pharmacodynamic[19] information (e.g., blood-brain barrier penetration, degree and duration of receptor occupancy) that can influence the choice of a drug candidate and optimize hypothesis testing," (Ex. 1012 at 20). To demonstrate its value, Hargreaves employed the methodology and tracer to help (1) quantify the NK-1 receptor occupancy achieved by various doses of aprepitant, (2) define aprepitant's dose-response relationship,[20] and (3) predict effective dosing regimens for aprepitant's

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[18] Pharmacokinetic ("PK") parameters are drug-specific and include properties like blood-brain barrier penetration, clearance, volume of distribution, bioavailability, absorption rate, half-life. (*See, e.g.*, Ex. 1012 at 20.)

[19] Pharmacodynamics ("PD") parameters are drug- and receptor-specific and include properties like degree and duration of receptor occupancy, affinity, potency, efficacy, and receptor selectivity. (*See, e.g.*, Ex. 1012 at 20.)

[20] The "dose-response relationship" is the quantification of a drug's specific association between (i) the dose of the drug, (ii) the plasma concentration of the drug created by that dose, (iii) the degree of receptor occupancy achieved by that dose, and (iv) any observed clinical effect attributable to that dose. (*See, e.g.*, Ex. 1012 at 18, 23-24.)

subsequent clinical trials. (Ex. 1012 at 18-19.) Importantly, a POSA would have known that dose-response relationships are complex, drug-specific associations that cannot be extrapolated onto other drugs, regardless of whether the drugs-at-issue are in the same class of compounds (e.g., both are NK-1 receptor antagonists) or have the same mechanism of action (e.g., both use NK-1 receptor antagonism), etc. (Ex. 1012 at 20; Ex. 1009 at ¶ 853.) Therefore, it is my opinion that a POSA would have understood Hargreaves as teaching that neither aprepitant's dose-response relationship, nor its required degree of receptor occupancy for achieving consistent clinical benefits in the treatment of CINV, could be used to reasonably predict therapeutically effective amounts for different NK-1 receptor antagonists – let alone netupitant.

153. In fact, as I explain in detail below, Hargreaves teaches a POSA that to define the dose-response relationship of a NK-1 receptor antagonist that is not aprepitant, the POSA would need to conduct a new study using Hargreaves's disclosed methodology and tracer. Put another way, Hargreaves expressly does not teach a POSA to just assume that doses of other NK-1 receptor antagonists will be required to achieve the same degree of receptor occupancy as aprepitant.

a. Background Information

154. By way of background, "receptor occupancy" describes the percentage of available receptors on a cell that are occupied by a signaling molecule (ligand) at

any given time. Receptor occupancy is the percentage of target receptors bound by a ligand at a given concentration, determined by ligand concentration and affinity (KD). Occupancy influences pharmacological effect, but the occupancy-response relationship depends on ligand efficacy (agonist, partial agonist, antagonist), the presence of spare receptors, downstream signaling, and receptor desensitization. Thus, higher occupancy often increases the effect up to a point, but maximal response can occur below 100% occupancy, and different ligands can produce different effects at the same occupancy. Furthermore, pharmacokinetics and tissue distribution also affect *in vivo* relevance.

155. Conversely, "binding affinity" is a measure of how long a given antagonist binds to a given receptor. Therefore, binding affinity should not be confused with receptor occupancy, which (as discussed above) is a measurement of how many receptors are occupied with a given drug substance at a given time and is necessarily impacted by the amount of drug that is administered and the frequency of its administration.

b. Methodology for PET Studies Using Novel Tracer of NK-1 Receptor Activity

156. In my opinion, a POSA would have known that the purpose of Hargreaves was to illustrate the value of Merck's [^{18}F]SPA-RQ tracer, not investigate aprepitant's dose-response relationship. As I briefly explained above,

Hargreaves was essentially a proof-of-concept study meant to establish the utility of Merck's recently developed, radioactive, NK-1 receptor-specific tracer, [^{18}F]SPA-RQ. (Ex. 1012 at 18-19.) In fact, it expressly discloses as much, stating that "[t]he goals of this review are to describe the localization of the SP-NK_1 receptor system in animals and humans, as determined by . . . PET studies, and to discuss the experience with [^{18}F]SPA-RQ as a tool to facilitate" the clinical development of NK-1 receptor antagonists for treatment of CINV. (Ex. 1012 at 19.) Accordingly, a POSA would have recognized that Hargreaves's aprepitant-specific PET studies were only conducted to exemplify how [^{18}F]SPA-RQ "permits real-time imaging of receptor occupancy in living human subjects via PET imaging," and the "quantification of NK_1 receptor occupancy with various doses of [NK_1 receptor antagonists] and thereby helps to define the degree and duration of receptor occupancy required to achieve consistent antidepressant / antiemetic effects." (Ex. 1012 at 18-19.) Therefore, in my opinion, Hargreaves would have taught a POSA that to determine the dose-response relationship of a different NK-1 receptor antagonist (e.g., netupitant) the POSA would need to use Hargreaves's methodology and tracer (not its aprepitant-specific data) and either conduct, or possess data from, the following studies:

(1) a successful dose-ranging clinical trial for treating CINV with the study drug;

(2) plasma concentration measurements for the study drug in patients treated with the dosing regimens used in the CINV trial; and

(3) Hargreaves's PET studies replicated with doses of the study drug (instead of aprepitant)

(*See* Ex. 1012 at 20-23.)

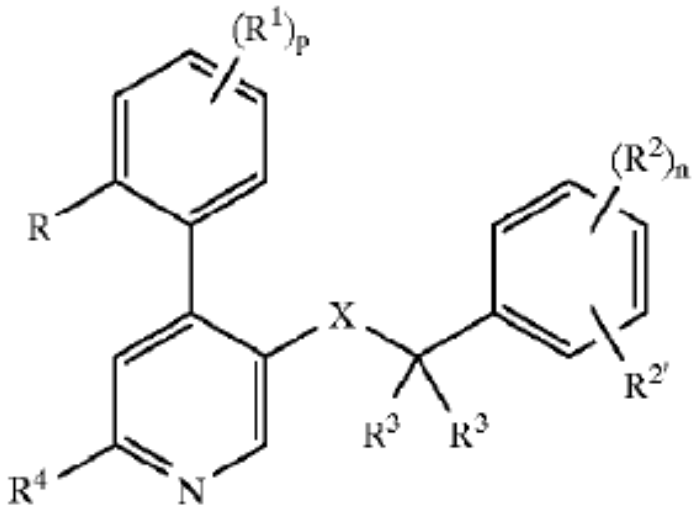
157. However, as of November 2009, netupitant's relationship between dose, plasma concentration, and NK-1 receptor occupancy was completely unknown. In fact, a POSA would have no knowledge whatsoever regarding netupitant's various PK or PD properties associated with its dose-response relationship, such as its blood-brain barrier penetration in humans, degree and duration of receptor occupancy, or relationship between blood concentration, response, and time – let alone whether it is safe or effective in humans. As a result, a POSA would have known that they would have to conduct each of those three studies themselves to determine netupitant's dose-response relationship and thus the NK-1 receptor occupancy achieved by a specific dose of netupitant 72 hours after administration (*see* Section VIII.A).

3. Bös (Ex. 1014)

158. Bös is U.S. Patent No. 6,297,375 and 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.)

159. The Bös patent describes a large class of pyridine compounds, encompassing millions of individual compounds. 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 position in the general formula. (*Id.*) The number of iterations of substitutions totals more than a million potential compounds, including netupitant among these millions of compounds.

160. The Bös patent also describes a long list of different potential 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).)

161. Accordingly, Bös roughly lists millions of NK-1 receptor antagonists and a vast number of afflictions that any one of those millions of antagonists might potentially be therapeutic. (Ex. 1014 at 2:01-65.) Importantly, among the long list of potential uses of these compounds, nausea is not included or otherwise mentioned. Instead, only emesis is described. (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.").)

162. In addition, Bös lacks human clinical data and provides only data from *in vivo* animal studies and from *in vitro* Chinese hamster ovary (CHO) cells in which human NK-1 receptors were introduced. (Ex. 1014 at 13:24-67.) The *in vivo* animal model studies were exploratory for anxiety or central nervous system distribution (gerbil foot tapping), motion sickness (*suncus murinus*, more commonly called a shrew), and emesis (ferrets) using NK-1 receptor antagonists. (Ex. 1014 at 13:40-67.) While the tests showed that NK-1 receptor antagonists induced behaviors in gerbils and blocked emesis in ferrets and *suncus murinus* with similar potency, none of these tests could evaluate netupitant's efficacy for nausea. (Ex. 1014 at 13:51-67.) For example, inducing motion sickness in a *suncus murinus* shrew is not a model for assessing the nausea resulting from chemotherapy. Instead, motion sickness results from a mismatch between the sensory input from the inner ear and the eyes, which may lead to vomiting. Moreover, Bös makes no mention of aprepitant, nor does Bös compare any of its disclosed compounds to aprepitant.

163. In my experience, blocking emesis in ferrets is useful for early screening, but it is not strong evidence that an NK-1 receptor antagonist will work in humans for CINV, much less chemotherapy-induced nausea. First, NK-1 receptor structure differs between species, and drug affinity for NK-1 receptors can differ dramatically across species, resulting in some NK-1 antagonists that work in

ferrets binding poorly to the human receptor. Second, ferret models do not reflect the complexity of CINV in humans. While ferret chemotherapy models can replicate acute emesis, they do not fully replicate delayed CINV and do not model nausea well (as nausea is generally difficult to measure in animals). Therefore, blocking emesis in ferrets does not guarantee adequate human CNS penetration, sufficient human NK-1 receptor occupancy, or an appropriate PK profile for delayed CINV.

VII. CLAIM CONSTRUCTION

164. 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.

A. Claims Require Treating Chemotherapy-Induced Nausea to a Statistically Significant Degree Relative to Baseline

165. Independent claims 1, 2, and 4 recite a "method of treating . . . (CINV)." (Ex. 1002 at claims 1, 2, and 4.) Dependent claims 34, 35, 47, and 48, which ultimately depend from claim 1, further recite that the claimed regimen (which includes a single dose of netupitant or a pharmaceutically acceptable salt thereof) is "effective to prevent nausea" and/or "reduce the severity

of nausea" in the patient. (Ex. 1002 at claims 34, 35, 47, and 48.) Dependent claims 58 and 59, which ultimately depend from claim 4, further recite that the claimed regimen is "effective to prevent or reduce the severity of nausea" in the patient. (Ex. 1002 at claims 58 and 59.) In my opinion, a POSA would have understood that treating, preventing, and reducing should be construed to require that the claimed regimen achieves the improvement in the desired effect (treating CINV and preventing or reducing the severity of nausea, as applicable) to a statistically significant degree as compared to baseline.

166. Claim 1 provides:

> **1.** A method of treating chemotherapy induced nausea and vomiting (CINV) comprising administering to a subject receiving chemotherapy a regimen of palonosetron, netupitant and dexamethasone.

(Ex. 1002 at claim 1.)

167. Claims 19 and 21, which connect claim 1 to claims 34 and 35, provide:

19. The method of claim **1**, wherein:
a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy;
b) said regimen comprises a single administration of netupitant or pharmaceutically acceptable salt thereof and a single administration of palonosetron or pharmaceutically acceptable salt thereof;
c) said netupitant or pharmaceutically acceptable salt thereof and said palonosetron or pharmaceutically acceptable salt thereof are administered concomitantly and prior to said chemotherapy, without administering a second dose of either for at least five days after said chemotherapy; and
d) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

21. The method of claim **19**, wherein:
a) said netupitant is administered orally as the free base in a dose of about 300 mg;
b) said palonosetron is administered orally as palonosetron hydrochloride in a dose of about 0.50 mg based on the weight of the free base; and
c) said netupitant and palonosetron are administered as a single unit dosage form less than 2 hours prior to said chemotherapy.

(Ex. 1002 at claims 19 and 21.)

168. Claims 34 and 35, which depend from claim 21, provide:

34. The method of claim **21**, wherein:
a) said chemotherapy is highly emetogenic chemotherapy; and
b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

35. The method of claim **21**, wherein:
a) said chemotherapy is moderately emetogenic chemotherapy; and
b) said regimen is effective to prevent nausea or reduce the severity of nausea in said patient during the acute and delayed phases of said CINV.

(Ex. 1002 at claims 34 and 35.)

169. Claims 47 and 48, which depend from claim 35, provide:

47. The method of claim **35**, wherein said regimen is effective to prevent nausea in said patient following the administration of said chemotherapy.

48. The method of claim **35**, wherein said regimen is effective to reduce the severity of nausea in said patient following the administration of said chemotherapy.

(Ex. 1002 at claims 47 and 48.)

170. Claim 2 provides:

> **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.

(Ex. 1002 at claim 2.)

171. Claim 4 provides:

> **4**. A method of treating chemotherapy induced nausea and vomiting (CINV) comprising inducing in a subject receiving chemotherapy blood levels of palonosetron and netupitant effective to treat said CINV.

(Ex. 1002 at claim 4.)

172. Claim 54, which connects claim 4 to claims 58 and 59, provides: from claim

> **54**. The method of claim **4**, wherein:
> a) said treatment of CINV is defined as no emetic episodes and no use of rescue medication following said chemotherapy
> b) said blood levels are induced by an intravenous anti-emetic regimen administered prior to said chemotherapy; and
> c) said regimen is effective to treat said CINV for a five day period after said chemotherapy.

(Ex. 1002 at claim 54.)

173. Claims 58 and 59, which depend from claim 54, provide:

> **58**. The method of claim **54**, wherein said chemotherapy is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

> **59**. The method of claim **54**, wherein said chemotherapy is moderately emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

(Ex. 1002 at claims 58 and 59.)

174. A POSA would also understand that the claimed method of treatment is required to show a statistically significant improvement in efficacy relative to a baseline. The specification of the ’357 patent expressly states that “when a ***treatment*** is described herein, it will be understood that the treatment shows efficacy to a ***degree of statistical significance***.” (Ex. 1002 at 8:31-34 (emphasis added).) A method of preventing nausea is a method of treatment in the context of the ’357 patent. (*Id*., 8:5-23.) The terms “treating” and “treatment” also “refer to the medical management of a patient with the intent to . . . prevent a disease . . . .” (*Id.* at 8:5-8.) This also includes “preventative treatment, that is, treatment directed to minimizing or partially or completely inhibiting the development of the associated disease, pathological condition, or disorder . . . .” (*Id.* at 8:16-20.) As Dr. Peroutka agrees, if a treatment is not to a degree of statistical significance compared to baseline, a POSA would not be able to trust that the regimen had a real effect and that it was not due to random chance. (*See* Ex. 2086 at 24:9-16.)

175. The ’357 patent specification also provides guidance on how a given result was evaluated for statistical significance. The specification expressly states that “[u]nless otherwise specified, the level of statistical significance is $p<0.05$.” (Ex. 1002 at 8:27-28.) In other words, this p-value shows that there was only a 5% (or 1 in 20) chance that this result is a false positive and only occurred by chance.

Notably, and as Dr. Peroutka agrees, a p-value of <0.05 is consistent with the standard of statistical significance that is used by the FDA to evaluate the robustness of the data in clinical studies that are included as part of New Drug Applications to ensure that the effect is real and not due to random chance. (Ex. 2086 at 24:9-16, 25:13-18, 29:8-16, 183:17-184:3; *see also* Ex. 2085 at 15.)

176. The patent specification's requirement that the claimed methods of treating, preventing, or reducing the severity of nausea show a statistically significant improvement in efficacy over baseline is also consistent with the general principle that physicians do not want to treat patients with an ineffective therapy. I closely follow this principle in my own clinical practice. Statistical significance provides me with confidence that the claimed three-drug regimen of netupitant/palonosetron/dexamethasone will likely result in the intended treatment effect on both nausea and vomiting, and be a clinically meaningful improvement over the two-drug regimen of palonosetron and dexamethasone.

VIII. REBUTTAL TO DR. PEROUTKA'S OPINIONS

177. For the reasons discussed below, I disagree with the opinions provided by Dr. Peroutka in his declaration and deposition testimony in this proceeding. (*See generally*, Ex. 1009; Ex. 2086.) I identify and discuss those opinions below and provide my responses to them.

178. In my opinion, and for the reasons discussed below, Dr. Peroutka fails to consider the prior art as a whole, including what the prior art would have taught a POSA, both individually and collectively. Similarly, Dr. Peroutka fails to appreciate that the development of new NK-1 receptor antagonists and new treatments for chemotherapy-induced nausea were in a highly unpredictable field with an extraordinarily high rate of failure.

A. The Cited References Do Not Disclose All of the Limitations

179. Claims 24, 29, 36, 45, and 55 recite "wherein said netupitant occupies at least 70% of said patient's striatum NK_1 receptors ninety-six hours after said administration." (*See, e.g.*, Ex. 1002 at claims 24, 29, 36, 45, 55.) Dr. Peroutka opines that various combinations of Herrstedt, Bös, Hargreaves, Herrington, Bonadeo, and Aloxi discloses this limitation. (*See, e.g.*, Ex. 1009 at ¶¶ 1315-23.) I disagree with his opinion.

180. Despite stating that Herrstedt helps disclose this claim limitation regarding netupitant's degree and duration of NK-1 receptor occupancy, Dr. Peroutka does not actually cite to Herrstedt for support while opining on the issue. (*See generally* Ex. 1009 at ¶¶ 1315-23.) This makes sense as Herrstedt does not mention netupitant, let alone administering a particular amount of netupitant. Likewise, Herrstedt does not discuss the relationship between a therapeutically effective dose, plasma concentration, and degree of NK-1 receptor occupancy in

the human striatum for any NK-1 receptor antagonist (let alone netupitant or 96 hours after administration.

181. In Paragraph 853, Dr. Peroutka cites an observation in Bös that netupitant has "excellent CNS penetration," but he fails to explain why a POSA would have reasonably expected Bös's observation from *in vivo* ***testing in gerbils*** (foot-tapping behavior) into translate to "excellent CNS penetration" in ***humans***.[21] (*See* Ex. 1009 at ¶¶ 853, 883.) Next, Dr. Peroutka opines that "[a] POSA would have understood that orally-administered netupitant provides the desired therapeutic effect by entering systemic circulation after administration and crossing the blood brain barrier to enter the central nervous system." (*See, e.g.*, Ex. 1009 at ¶¶ 1112, 1318.) However, Bös does not discuss any human trial data (*e.g.*, a human PET study, CSF sampling, clinical PK modeling, or *in vitro* human blood-brain barrier transporter assays) that could have possibly provided a POSA with an

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[21] In general, animal models are used as a signal to indicate that a study drug could potentially exhibit similar properties when administered to humans, and a significant amount of additional clinical research would need to be conducted to determine if a given effect translates to humans. (*See, e.g.*, Ex. 1012 at 18 (noting "some interspecies differences in the expression of NK receptors").)

understanding of netupitant's blood-brain barrier permeability in humans or its ability to penetrate the human CNS. (*See generally* Ex. 1014.) Therefore, Bös would not have taught a POSA anything about whether netupitant crosses the blood-brain barrier to enter the human central nervous system, let alone that orally-administered netupitant could do so to provide the claimed therapeutic effect. Accordingly, Hoffmann would not have taught POSA anything about a therapeutically effective dose of netupitant that would occupy at least 70% of NK-1 receptors in the human striatum for 96 hours.

182. In Paragraphs 1114 and 1115, Dr. Peroutka discusses Hargreaves, including its positron emission tomography ("PET") imaging studies and its prediction of NK-1 receptor occupancy at aprepitant doses used in clinical trials involving patients with depression and CINV. (*See* Ex. 1009 at ¶¶ 1114-15, 1320-21; Ex. 1012 at 23.) Dr. Peroutka opines that "Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum." (Ex. 1009 at ¶¶ 1114, 1320.) However, Hargreaves only evaluated the distribution of NK-1 receptors in the CNS of healthy male volunteers using the [^{18}F]SPA-RQ tracer prior to and after 14-day treatment with placebo or increasing doses of aprepitant (10-300 mg) to establish aprepitant's plasma concentration vs. receptor occupancy relationship. (*See* Ex. 1012 at 23.) Importantly, these findings were all specific to aprepitant's relationship between

dose, plasma concentration, and NK-1 receptor occupancy, which is dependent on its unique "pharmacokinetic and pharmacodynamic information (e.g., blood-brain barrier penetration, degree and duration of receptor occupancy)." (*See* Ex. 1012 at 20.)

183. In my opinion, Dr. Peroutka fails to address that Hargreaves merely discusses aprepitant's dose-response relationship, which is exclusive to that specific drug (*i.e.*, aprepitant) and is not generally applicable to every drug in its class (*i.e.*, all NK-1 receptor antagonists). (*See* Ex. 1012 at 20.) Rather, the dose-response relationship is a complex association based on the evaluation of various interrelated information, *e.g.*, aprepitant's unique pharmacokinetics ("PK")[22] and pharmacodynamics ("PD")[23], PET imaging data, and successful clinical trial data. (*See* Ex. 1012 at 20, 23.) The purpose of determining the dose-response

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[22] PK parameters are drug-specific and include properties like blood-brain barrier penetration, clearance, volume of distribution, bioavailability, absorption rate, and half-life. (*See, e.g.*, Ex. 1012 at 20.)

[23] PD parameters are drug- and receptor-specific and include properties like degree and duration of receptor occupancy, affinity, potency, efficacy, and receptor selectivity. (*See, e.g.*, Ex. 1012 at 20.)

relationship is to help guide dosing regimens for the ***same*** drug in its future trials. In my opinion, a POSA who read the Hargreaves study would have understood that to determine the "relationship between dose, plasma concentration, and NK-1 receptor occupancy" for netupitant, a POSA would need to conduct an entire study substantially similar to Hargreaves, including access to clinical trial data and netupitant-specific PET scans. Only this detailed approach would allow a POSA to quantify NK-1 receptor occupancy with various doses of netupitant and thereby help to define the degree and duration of receptor occupancy required to achieve consistent clinical effects.

184. Netupitant's relationship between dose, plasma concentration, and NK-1 receptor occupancy was completely unknown in November 2009. In fact, a POSA would have known nothing about netupitant's various PK or PD properties that are associated with its dose-response relationship **in humans**, such as its blood-brain barrier penetration, degree and duration of receptor occupancy, or relationship between blood concentration, response, and time – let alone whether it is safe or effective in humans. On the contrary, Hargreaves reported ***aprepitant****'s* NK-1 receptor occupancy for only 6 hours, beginning 24 hours after aprepitant administration and ending 6 hours later (*i.e.*, 30 hours after aprepitant administration). (*See* Ex. 1012 at 23 ("6-hour duration of imaging," "daily doses"

of aprepitant, and "trough concentration following treatment"[24]).) This data would not have disclosed to a POSA what aprepitant's NK-1 receptor occupancy was **96** hours after administration, much less what netupitant's NK-1 receptor occupancy was **96** hours after administration, as required by the claim. (*See* Ex. 1012 at 21-22.)

185. Dr. Peroutka attempts to fill this gap by citing to Bös and opining that "seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant." (Ex. 1009 at ¶¶ 1116, 1322 (citing Ex. 1014 at 19:7-38).) But Bös does not disclose any information about netupitant's half-life in a patient (*i.e.*, a human) and certainly does not disclose that netupitant's half-life in humans is prolonged or approximately 72 (or 96) hours. (*See* Ex. 1014 at 19:7-38; Ex. 1009 at ¶ 100; *see generally* Ex. 1014.) Instead, Dr. Peroutka's cited portion of Bös merely discusses netupitant's half-life in three different species of animals: (1) 30-hours in gerbils (Ex. 1014 at 18:64-19:09), (2)

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[24] "Trough level" or "trough concentration" is the concentration reached by a drug immediately before the next dose is administered. Aprepitant is administered once daily so its trough concentration is reached 24 hours after administration.

24-hours in rats (Ex. 1014 at 19:31-19:38), and (3) 18-hours in dogs (*id.*). (*See* Ex. 1014 at 18:64-19:38.) Despite the discrepancy between animal models and humans, Dr. Peroutka does not explain how his citation to the animal data in Bös provides any support for his conclusion that netupitant's half-life in humans was "known" to be "prolonged" – much less an approximation of netupitant's half-life in humans. (Ex. 1009 at ¶¶ 100, 1116, 1322.) Therefore, in my opinion, Bös neither expressly nor implicitly teaches netupitant as having a long half-life in humans and thus would not have disclosed any pertinent information to a POSA regarding the limitation at issue here.

186. Dr. Peroutka similarly opines that a POSA would have reasonably expected that there would still be high occupancy of the striatum NK_1 receptors at 72 hours due to netupitant's long half-life. (Ex. 1009 at ¶ 1116.) However, netupitant's half-life is not causally associated with its degree and duration of NK-1 receptor occupancy (*see, e.g.*, Ex. 1012), and Dr. Peroutka has not explained why he believes otherwise (*see* Ex. 1009 at ¶¶ 100, 1116). Rather, netupitant's half-life in humans comprises just one of the many pharmacokinetic and pharmacodynamic properties (*e.g.*, blood-brain barrier penetration in humans, clearance rate, bioavailability, absorption rate, receptor affinity, potency, plasma concentration, etc.) associated with the degree and duration of NK-1 receptor occupancy achieved by any particular dosage of netupitant.

187. Importantly, Dr. Peroutka does not (and cannot) point to any prior art that discloses what a therapeutically effective amount of netupitant would be, such that when it was administered to a human, it would result in the specific claimed amount of receptor occupancy over the specific claimed timeframe. (*See* Ex. 1009 at ¶¶ 1116, 1322 (citing Ex. 1002 at 4:37-51).) Similarly, Bös does not disclose what a therapeutically effective amount of netupitant would be for treating ***both*** nausea and vomiting in a human in need thereof, nor a dose of netupitant that would occupy at least 70% of the NK-1 receptors in the striatum of a human for 96 hours (or 72 hours).

188. Therefore, in my opinion, Hargreaves does not disclose that a therapeutically effective dose of netupitant (or any other NK-1 receptor antagonist) would occupy at least 70% of NK-1 receptors in the human striatum for at least 72 hours (or 96 hours). Instead, a POSA would have known that the disclosures in Hargreaves are limited to aprepitant and provide no information whatsoever on what therapeutically effective dose of netupitant would result in the limitation recited in part (a). Furthermore, a POSA would have recognized that Hargreaves's methodology (effective dose vs plasma concentration vs human PET occupancy for aprepitant) supports the fact that to reasonably predict a specific degree and duration of NK-1 receptor occupancy for any study drug other than aprepitant, a POSA would need efficacy, dosing, and plasma concentration data from clinical

trials as well as human PET imaging data (or equivalent data thereof) – *i.e.*, the same types of data utilized by the Hargreaves study. Accordingly, Hargreaves is silent regarding netupitant, and in fact, I am aware of no prior art showing a netupitant dose that yields ≥70% striatal NK-1 occupancy for 96 hours.

189. Lastly, Dr. Peroutka asserts that the '357 patent specification supports his opinion that the "at least 70%" occupancy limitation is a "characteristic of netupitant itself." (*See* Ex. 1009 at ¶¶ 1116, 1322 (citing Ex. 1002 at 4:37-51).) I disagree with Dr. Peroutka. In my opinion, the statement in the specification that he cites discloses only that after administering a single dose of netupitant, the dose's occupancy of the striatum's NK-1 receptors will eventually peak and then slowly decline such that 96 hours after administration, the amount of total NK-1 receptor occupancy in the striatum that occurs following that dose has decreased only by about 20 to 30%.[25] Importantly, the specification does not disclose that administering a single dose of netupitant in any amount will always result in netupitant occupying at least 70% of the striatum's NK-1 receptors 72 hours after

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[25] As a hypothetical illustrative example, if a given dose of a drug were to initially occupy 65% of a certain receptor, then a 20% decrease in receptor occupancy would mean that 52% of the receptors were then still occupied.

administration. (*See, e.g.*, Ex. 1002 at Example 4, Figure 5.) Instead, the specification provides the inventors' "Netupitant PET Receptor Occupancy Study,"[26] which discloses netupitant's dose-receptor occupancy relationship and thus allows a POSA to determine whether a given dose of netupitant results in occupancy of at least 70% of the striatum's NK-1 receptors 72-hours after administration. (*See* Section VI.B.2; *compare* Ex. 1002 at Example 4, *with* Ex. 1012.) And as shown in Figure 5, for example, a dose of 300 mg of netupitant would occupy at least 70% of the NK-1 receptors in the striatum 72 hours after administration, whereas a dose of 100 mg of netupitant would not. (Ex. 1002 at Figure 5.) Therefore, my opinion is that the claimed 70% receptor occupancy is a function of netupitant concentration in the body at a given time, which in turn depends on dose and other complex pharmacological and pharmacokinetic factors, rather than a mere function of netupitant. (*Id.*)

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[26] Notably, the inventors conducted a PET receptor occupancy study on netupitant – rather than just relying on the Hargreaves study's disclosures about aprepitant – because the results of the dose-response relationship are drug-specific.

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

190. 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 ¶¶ 843, 1003, 1090, 1108, 1124, 1140, 1156, 1313.) His analysis assumes that a POSA would have started with a reference discussing triple therapy (*e.g.*, Herrstedt),[27] then identified references disclosing netupitant (*e.g.,* Bös), and finally altered triple therapy by removing aprepitant and substituting netupitant. As I describe below, Dr. Peroutka fails to consider the paths a POSA would have followed given the problem facing the POSA.

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[27] Dr. Peroutka relies heavily on the Herrstedt article (Ex. 1010) in forming his opinions, citing it repeatedly throughout his declaration. (*See, e.g.*, Ex. 1009 at ¶¶ 111-15, 843-1328, 1370, 1393, 1396-97.) Notwithstanding this, Dr. Peroutka testified that Herrstedt contains statements that he "would not agree with" and would "have to see the primary data to support." (*See, e.g.*, Ex. 2086 at 52:02-60:08.)

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

191. Dr. Peroutka did not identify a problem with the CINV treatments existing as of November 2009 that a POSA would have been trying to solve. In my opinion, a POSA would first identify a problem to be solved and then focus their research on developing a potential solution. 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.

192. As I explained in the background section above 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.) A POSA would have understood that during the relevant time frame of November 2009 (as I defined above in Section IV), there were available CINV treatments that effectively controlled emesis. For example, the use of aprepitant in triple therapy (dexamethasone, 5-HT_3 receptor antagonist, aprepitant) improved the control of acute and delayed emesis as compared to standard therapy (dexamethasone and 5-HT_3 receptor antagonist). (*See, e.g.*, 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").)

193. Available clinical trial data for triple therapy (*see* Section VI.A) indicated that triple therapy was not effective in controlling nausea. 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)).) And as I discussed in detail above, the Emend® Label expressly states that aprepitant does not provide any statistically significant improvement in nausea. (*See* Section VI.A.2; *see also* Ex. 1016 at 2086 ("According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea . . . .").)

194. Therefore, a POSA considering 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.

2. Dr. Peroutka Fails to Analyze the Various Paths a POSA Could Have Taken To Find an Improved Treatment for Nausea

195. As I explained above, a POSA considering the potential treatments for CINV would have understood that the problem they faced was the need for a treatment for CINV with improved a 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. Nor does

Dr. Peroutka establish that a POSA would have looked to replace aprepitant in triple therapy with netupitant to solve this problem. As I explain below, a POSA would have instead looked to other classes of drugs and/or other drug combinations for the potential control of nausea.

196. Given that triple therapy was known to be effective against emesis following chemotherapy, one path that a POSA would have considered was adding a fourth drug that may be useful in the control of chemotherapy-induced nausea. (*See, e.g.*, 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 (*i.e.*, NK-1 receptor antagonism) 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; *see also* 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 in the NCCN Antiemesis Guidelines 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.)

197. As I explained above in Section V.C., promising antinausea agents with different mechanisms of action than aprepitant (such as olanzapine, gabapentin, dronabinol, nabilone, metoclopramide, prochlorperazine and/or promethazine) 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; Ex. 1019 at 1147.) For example, publications at that time had reported that the "most promising" antiemetic 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." (*See, e.g.*, Ex. 1010 at 149.)

198. In fact, post-2009 research 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, the combination of olanzapine plus triple therapy (*i.e.*, olanzapine plus dexamethasone, aprepitant or fosaprepitant, and a 5-HT_3–receptor antagonist) as compared 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, 138.) 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, 138.) Overall, during the 120-hour period, 37% of patients who received olanzapine plus triple therapy reported "no nausea," compared with 22% of patients who received triple therapy. (Ex. 2039 at 134, 138.)

199. 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 and 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 further 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. (*See* 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.

200. 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. (*See* Ex. 2036 at 525; Ex. 2037 at 578, 590 (listing dronabinol and nabilone).)

201. 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; Ex. 2042, Ex. 2043.) Dronabinol was indicated for "nausea and vomiting associated with cancer 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 also 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 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 unique mechanism of action. (*See* 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.").)

202. Though cannabinoids were "slightly better than conventional antiemetics," conventional antiemetics, like metoclopramide and phenothiazines, had different mechanisms of action that a POSA could consider for adding to triple therapy. (*See* Section V.C.4-5.) As discussed above, Section V.C.4-5, metoclopramide and phenothiazines (*i.e.*, prochlorperazine) were listed as options for low emetic risk chemotherapy in the 2009 NCCN Antiemesis guidelines. (Ex. 2037 at 577.) Moreover, metoclopramide and phenothiazines (*i.e.*, prochlorperazine, promethazine) were listed as options clinicians could use for breakthrough treatment for chemotherapy-induced nausea and vomiting. (Ex. 2037 at 578.)

203. In sum, my opinion is that in November 2009, a POSA would have recognized that the prior art identifies a specific problem with the current gold

standard treatment for CINV, *i.e.*, triple therapy does not effectively reduce the degree of chemotherapy-induced nausea experienced by patients. In addition, a POSA would have understood that the prior art provides very little guidance on how to develop a successful treatment against nausea because the pathophysiology of chemotherapy-induced nausea and its related mechanisms of action were not well defined. In spite of this overall uncertainty in the field, a POSA would have still recognized that the prior art had identified the following options as the most promising approaches to solving triple therapy's "nausea" problem:

- Investigating drugs that have different mechanisms of action and are specifically identified as promising antinausea agents that could be added as a fourth drug to triple therapy
    - For example, the prior art specifically identified drugs like olanzapine, gabapentin, dronabinol, nabilone, metoclopramide, prochlorperazine and/or promethazine as promising antinausea agents, (*see* Section V.C)
- Investigating drugs that may block neuroreceptors specifically identified by the prior art as involved in the emetic reflex arch and thus potentially involved in the pathogenesis of chemotherapy-induced nausea (not 5-HT_3 and NK-1 receptors)

  - For example, the prior art specifically identified, *e.g.*, dopamine, serotonin-1, serotonin-2, serotonin-4, serotonin-5, serotonin-6, serotonin-7, neurokinin-2, neurokinin-3, acetylcholine, GABA, histamine, cannabinoid, opioid, endorphin, and muscarinic receptors as involved in the emetic reflex arch and potentially involved in the pathogenesis of chemotherapy-induced nausea (*see* Section V.A.4; Section V.B.4-5)

- Investigating drugs in the corticosteroid class which the prior art specifically identified as promising antinausea agents that have not been adequately researched
  - For example, the prior art specifically identified that higher doses of corticosteroids, a different dosing regimen for dexamethasone, and corticosteroids other than dexamethasone as potential approaches to solving nausea (*see* Section V.B.2.a)

However, other than these specifically identified approaches for potentially developing a successful treatment for nausea, the prior art gave a POSA no indication as to which of the many possible options or combination of options were likely to be successful due to the general lack of knowledge regarding nausea and the unpredictability in the field. Furthermore, the prior art did not identify substituting aprepitant for another NK-1 receptor antagonist, especially not

netupitant, as a potential option for treating chemotherapy-induced nausea. To the contrary, a POSA would have known that the prior art consistently taught away from utilizing NK-1 receptor antagonists for treating nausea because it was believed that NK-1 receptors were not important to the pathophysiology of nausea. Therefore, the teachings of the prior art would have led a POSA to focus their investigation on the readily-identified, proposed solutions to triple therapy's lack of efficacy against nausea – like adding olanzapine as a fourth drug to triple therapy – and would have directed a POSA away from approaches that the references disclosed as being likely to fail – like replacing aprepitant with a different NK-1 receptor antagonist in triple therapy. (*See* Section V.C.)

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

204. As I explained above in Section VIII.B, Dr. Peroutka failed to consider the problem facing a POSA (*i.e.*, an improved treatment for cancer patients suffering from nausea following chemotherapy) and the various paths a POSA might have considered to solve it. Instead of performing this analysis, Dr. Peroutka assumed that a POSA would immediately seek to replace aprepitant in triple therapy with another NK-1 receptor antagonist (specifically, netupitant). (*See, e.g.,* Ex. 1009 at ¶¶ 845, 996-1002, 1087-89, 1102-07, 1118-23, 1134-39, 1151-55, 1305-12, 1324-28.) But even if I were to assume (for the sake of

argument) that a POSA would start with triple therapy 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.

1. Dr. Peroutka Fails to Show that a POSA Would Consider Netupitant as Equivalent to or an Improvement over Aprepitant

205. At his deposition, Dr. Peroutka testified that a POSA would have no motivation to replace aprepitant for netupitant in triple therapy unless the POSA expected "that the change would provide similar or better patient outcomes." (Ex. 2086 at 293:19-294:10.) I agree with Dr. Peroutka that a POSA would have no reason to alter aprepitant-based triple therapy, which was the standard of care treatment in November 2009, unless the POSA had reason to expect that this change would actually provide a better patient outcome. As I explain below, Dr. Peroutka has not provided any evidence for his conclusion that a POSA would have expected that netupitant would be a "favorable alternative NK_1 receptor antagonist to aprepitant" (*see, e.g.*, ¶¶ 884, 1000) and a POSA would have "expected continued efficacy" based on the proposed substitution." (*See, e.g.*, Ex. 1009 at ¶¶ 997.) In fact, in November 2009, netupitant was a relatively new compound along with numerous other NK-1 receptor antagonists, with no available clinical data on its safety or efficacy in treating any condition in humans.

206. The reference relied upon by Dr. Peroutka as disclosing netupitant (Bös), does not include any comparative analysis between aprepitant and netupitant from which a POSA could draw any conclusions regarding their comparative clinical efficacy in treating nausea and vomiting. Bös lacks any human clinical data, and instead only provides data from *in vivo* animal studies and *in vitro* CHO cells (non-CNS cells derived from hamster ovaries) where human NK-1 receptors were expressed. (*See* Ex. 1014 at 18:42-19:38.) These were early exploratory *in vivo* studies on, among other things, potential uses for NK-1 receptor antagonists that used animal models for anxiety (gerbil foot tapping), motion sickness (suncus murinus), and emesis (ferrets). (*Id.* at 18:42-19:38.) None of these animal models were used to assess any potential efficacy of netupitant in controlling nausea. (*Id.* at 14:9-30, 18:42-19:38.)

207. In my opinion, Bös did not compare the relative efficacy of netupitant and aprepitant in treating emesis or nausea in humans. Moreover, the preclinical animal data in these references is limited to netupitant's effect on emesis. (*See generally* Ex. 1014.) A POSA would understand that this preclinical data in animals would not necessarily translate to efficacy in humans, especially with difficult-to-model conditions like the nausea and vomiting induced by chemotherapy. (*See also* Ex. 2086 at 37:6-11.)

208. During his deposition, Dr. Peroutka also opined that there is an "***80 percent***" probability that ***any*** NK-1 receptor antagonist that had "some preclinical data" showing bioavailability, CNS penetration, and a "half-life that's consistent with human intake" would have been equally (if not more) effective as aprepitant at treating CINV in humans. (*See* Ex. 2086 at 86:23-90:12.) I disagree with Dr. Peroutka. As an initial matter, he has not provided any evidence for his opinion. I also disagree with his opinion in view of the high failure rate between preclinical and clinical studies. (*See* Section VI.B.1, VIII.D.2.) In my opinion, just because both aprepitant and netupitant are members of the same drug class of NK-1 receptor antagonists, a POSA would not expect their efficacy to treat a given condition to be the same or comparable. Stated differently, just because two molecules are in the same drug class does not mean they will be "equivalent" in the sense of clinical efficacy.

209. Dr. Peroutka opines that a POSA would have had been motivated to substitute netupitant for aprepitant in triple therapy because netupitant's was "shown to be 'a potent and selective antagonist'" (*see, e.g.*, Ex. 1009 at ¶ 845) with "excellent CNS penetration." (*See, e.g., id.* at ¶¶ 862, 883.) Dr. Peroutka further opines that a POSA would conclude that netupitant would have been a "favorable alternative NK_1 receptor antagonist to aprepitant." (*See, e.g.*, *id*. at ¶¶ 854, 884.) I disagree with Dr. Peroutka's opinion for several reasons.

210. *First*, Dr. Peroutka has not offered any evidence comparing aprepitant and netupitant's physical, chemical, or pharmacological properties, nor any evidence of how those properties may potentially impact their respective affinities with the NK-1 receptor. (*See, e.g.*, Ex. 2086 at 240:25-241:3, 242:25-243:5, 253:7-255:15.) He likewise provides no analysis comparing netupitant's affinity, CNS penetration, half-life, and oral antagonism properties to those of aprepitant. (*See, e.g.*, *id.*) But regardless, oral antagonistic activity, binding affinity, and receptor occupancy would not inform a POSA as to whether netupitant is an improvement over aprepitant in controlling vomiting and nausea in patients living with cancer.

211. *Second*, "CNS penetration" is a trait common across many drugs classes (including NK-1 receptor antagonists) and describes whether a drug can cross into the central nervous system, which encompasses both the brain, brain stem, and the spine.[28] CNS penetration is also associated with treating a wide variety of disorders other than emesis, including depression, anxiety, Parkinson's disease, and Alzheimer's disease. (*See, e.g.*, Ex. 1014 at 3:64-4:14.) Dr. Peroutka fails to provide any reason that a POSA evaluating the CNS penetration data in

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[28] Notably, NK-1 receptors are located throughout the body, including the gastrointestinal tract, skin, and lungs, and are not limited to the CNS.

Hoffmann and Bös would believe that netupitant could be superior 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. Accordingly, a POSA could not predict or conclude based on these publications whether netupitant would have been a viable alternative to aprepitant in any sense, even for the discrete metric of CNS penetration.

212. "Oral antagonistic activity" refers to a drug's ability to have a desired antagonistic effect when ingested orally. As both aprepitant and netupitant can be administered orally, there was no advantage to using netupitant over aprepitant based solely on oral antagonistic activity.

213. Finally, "binding affinity" is a measure of how long a given antagonist binds to a given receptor. (*See also* Ex. 2086 at 254:2-10.) In my opinion, pharmacological properties such as CNS penetration, oral antagonistic activity, binding affinity, and allegedly "long half-life" (*see* Ex. 1009 at ¶ 997) for netupitant 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 drug of the same NK-1 receptor antagonist class, given that aprepitant had shown excellent efficacy against emesis. (*See, e.g.*, 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.”).) Dr. Peroutka never explains what constitutes a “long” half-life and how netupitant’s half-life compared to aprepitant. Dr. Peroutka claims that netupitant was “shown to potently and selectively inhibit the NK_1 receptor” (Ex. 1009 at ¶ 997) but does not explain how such selectivity would translate to efficacy in humans for emesis or nausea; nor does he compare the alleged selectivity of netupitant with aprepitant’s selectivity.

214. Furthermore, the data that is provided in Bös is not sufficient to demonstrate that netupitant is equivalent to or an improvement over aprepitant.

215. Dr. Peroutka cites Bös to opine that “netupitant was shown to potently and selectively inhibit the NK_1 receptor-induced foot tapping after oral administration, which was indicative of successful NK_1 receptor antagonism.” (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* animal studies. (*Id.*) For example, the foot tapping data indicates that the NK-1 receptor antagonist inhibits NK-1 receptor activation when an NK-1 agonist is administered. Foot tapping in gerbils would not provide any information to a POSA regarding the efficacy of the NK-1 receptor antagonist for use in emesis and/or nausea. Dr. Peroutka also provides no explanation of how foot tapping in gerbils would lead a POSA to conclude that netupitant could be effective in treating CINV in humans, let alone the nausea component of CINV. Moreover, Bös does not mention 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 ¶¶ 854, 884.) 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.

216. In my opinion, the preclinical data provided in Bös does not provide any reason to use the compound netupitant for treating nausea. Given that nausea is a subjective endpoint that generally relies on patient self-reporting, it is difficult (if not impossible) to measure in animal models, including those models used in Bös. Indeed, the only reliable way to determine if a given treatment may be effective for nausea in humans is to conduct human clinical trials. In my opinion and experience, animal nausea-related behaviors are poor proxies for a subjective human sensation, so they can misrepresent human experience. For example, animals differ from humans (and from each other) in emetic anatomy, central nervous system pathways, receptor distribution, and drug pharmacokinetics. In addition, in my opinion and experience, drugs can also change general activity or produce species-specific behaviors that mimic or mask nausea. Accordingly, and in my opinion, because humans report conscious, context-dependent sensations influenced by expectations and comorbidities, animal signals must be corroborated

by clinical studies (including patient-reported outcomes and objective biomarkers when available) to confirm relevance, dose-response, and safety. Moreover, given that the ’357 patent claims a method of treating, preventing, or reducing the severity of nausea in human subjects, a POSA would also consider safety data for a give drug, which Dr. Peroutka neglected to consider. (*See, e.g.*, Ex. 2086 at 126:17-24.) As a general rule, a doctor would not treat a patient with a drug that was not considered safe and effective and whose potential benefits did not outweigh its potential risks.

2. Dr. Peroutka Did Not Explain Why a POSA Would Have Selected Netupitant from Among Other NK-1 Receptor Antagonists with Pre-Clinical Data

217. In his declaration, Dr. Peroutka evaluated the NK-1 receptor antagonists with human clinical trial data (*i.e.*, aprepitant, casopitant) and then (out of many other possibilities) chose to evaluate one additional NK-1 receptor antagonist (netupitant) that had no human data at all. (*See* Ex. 2086 at 121:5-22, 123:9-13.) Dr. Peroutka’s reasoning for selecting netupitant for his evaluation – other than being “the subject of this patent dispute” (Ex. 2086 at 127:5-10) – is that netupitant was “known to have high selectivity and affinity for the NK-1 receptor, excellent oral activity, and excellent penetration into the central nervous system.”

(*See, e.g.*, Ex. 1009 at ¶ 77.) However, Hoffmann[29], a reference cited by Dr. Peroutka as a reference for U.S. Patent No. 8,623,826, discloses that "[f]ollowing random screening of our corporate library, a unique compound cluster of achiral aryl-substituted isoxazole derivatives was discovered which showed moderate affinity at the human NK_1 receptor." (Ex. 1011 at 1362.) Hoffmann states "this structural class, which displays simple achiral features, had previously not been described in the patent literature either as an NK_1 lead structure or as a pharmaceutically active chemical class per se." (Ex. 1011 at 1362.) Hoffmann then explains that the researchers generated additional data for 31 compounds in this compound class. (Ex. 1011 at 1362.)

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[29] Hoffmann is a research article from 2006 authored by Torsten Hoffmann, Michael Bös, and colleagues, titled "Design and Synthesis of a Novel, Achiral Class of Highly Potent and Selective, Orally Active Neurokinin-1 Receptor Antagonists." (Ex. 1011 at 1362.) Both Hoffmann and Bös are the work of a single research team working at Hoffmann-La Roche. (*Compare* Ex. 1011 at 1362, *with* Ex. 1014 at Cover.) Hoffmann discusses the "discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK_1) receptor antagonists." (Ex. 1011 at 1362.)

218. Nevertheless, Dr. Peroutka agreed that it would be "a reasonable thing to do" for a scientist to evaluate other NK-1 receptor antagonists that were known as of 2009. (*See* Ex. 2086 at 84:15-18.) By November 2009, there were numerous other NK-1 receptor antagonists under investigation (or that had been investigated) that provided comparable pre-clinical data, including but not limited to, the following compounds that a POSA could consider:

- ZD4974 (developed by AstraZeneca) (Ex. 2045 at 519 ("potent, orally available, NK_1-selective antagonist"))
- CGP-49823 (developed by Ciba-Geigy) (Ex. 2061 at 979 (possessing "high affinity . . . at the human NK-1 receptor and good oral bioavailability," and was found to be "active in the inhibition of . . . thumping behavior in gerbils"); Ex. 2046 at 347 ("potent, centrally and orally active NK_1 receptor antagonist"))
- Lanepitant (developed by Eli Lilly) (Ex. 2047 at 102 ("high-affinity, non-peptide, competitive NK-1 receptor antagonist that acts both peripherally and centrally"); *see also* Ex. 2061 at 979-80)
- LY686017 (developed by Eli Lilly) (Ex. 2048 at 1537 ("high-affinity, selective [NK-1 receptor] antagonist that is orally available and brain penetrant"))
- FK888 (developed by Fujisawa Pharmaceutical) (Ex. 2049 at 785

("very potent dipeptide NK_1 receptor antagonist"); *id.* at 788 ("FK888 is therefore a selective NK_1 receptor antagonist both *in vitro* and *in vivo*, and will be a useful tool for clarifying the role of [substance P] in physiological and patho-physiological conditions"))

- Vofopitant (developed by GSK) (Ex. 2050 at 540 ("potent and selective NK_1 receptor antagonist with high affinity for the human NK_1 receptor and potent antiemetic activity in various animal models of emesis"); *see also* Ex. 2051)
- Vestipitant (developed by GSK) (Ex. 2051 at 9)
- Orvepitant (developed by GSK) (Ex. 2057 at 1661, Table 4)
- Befetupitant (developed by Hoffmann-La Roche) (Ex. 1011 at 1)
- R116031 (developed by Janssen) (Ex. 2066)
- L-733060 (developed by Merck) (Ex. 2052)
- L-736281 (developed by Merck) (Ex. 2053 at 254)
- L-742,694 (developed by Merck) (Ex. 2053 at 260 ("novel, high affinity tachykinin NK_1 receptor antagonist whose binding kinetics produce prolonged receptor antagonism"))
- L-741,671 (developed by Merck) (Ex. 2053 at 254 ("high affinity for the human tachykinin NK_1 receptor"))

- L-737,488 (developed by Merck) (Ex. 2061 at 977 ("showed high *in vivo* activity"))
- TKA731 (developed by Novartis) (Ex. 2054 at 570 ("high affinity for the human NK_1-receptor"))
- NKP608 (developed by Novartis) (Ex. 2055 at 287, 291 ("potent and selective NK1 receptor antagonist"))
- CP-99994 (developed by Pfizer) (Ex. 2060 ("known to have reasonable affinity for the human-like tachykinin NK_1 receptor"); *see also* Ex. 2056)
- GR-82334 (developed by GSK) (Ex. 2060 ("known to have reasonable affinity for the human-like tachykinin NK_1 receptor"))
- GR-203040 (developed by GSK) (Ex. 2061 at 977 ("showed subnanomolar affinity for NK-1 receptor, metabolic stability and activity in the screening emesis test"))
- GR-205171 (developed by GSK) (Ex. 2061 at 977 ("showed subnanomolar affinity for NK-1 receptor, metabolic stability and activity in the screening emesis test")
- CP-122721 (developed by Pfizer) (Ex. 2050 at 543 ("As far as delayed emesis is concerned, a favourable profile of the NK_1 receptor antagonists has been shown"))

- CJ-17493 (developed by Pfizer) (Ex. 2058 at 7193 (displayed "high and selective affinity" for the human NK-1 receptor in IM-9 cells, and "potent activity" in the gerbil tapping model and in the ferret cisplatin-induced anti-emetic activity model))
- Ezlopitant (CJ-11974) (developed by Pfizer) (Ex. 2050 at 540-41 ("selective NK_1 receptor antagonist . . . which proved highly active in the ferret model of emesis"); *id.* at 543 ("As far as delayed emesis is concerned, a favourable profile of the NK_1 receptor antagonists has been shown . . . when used in combination regimens"))
- Maropitant (CJ-11,972) (developed by Pfizer) (Ex. 2059 at 281-82, 285 ("Maropitant was shown to be a potent and selective *in vitro* NK_1 antagonist, binding selectively at NK_1 receptors with long-lasting centrally mediated effects when administered *in vivo* to gerbils."))
- Dapitant (developed by Rhone-Poulenc Rorer) (Ex. 2061 at 975 ("possesses good activity *in vivo* on plasma extravasation models in rats . . . after oral administration"))
- SR-140333 (developed by Sanofi) (Ex. 2061 at 979 ("shows high affinity *in vivo*"))
- PD-154075 (developed by Parke-Davis) (Ex. 2061 at 979 (shows affinity for binding to the human NK_1 receptor and "displays a good

activity in *in vivo* tests . . . in a guinea-pig plasma protein extravasation model”))

- SSR240600 (developed by Sanofi-Aventis) (Ex. 2062 at 1171 (“new, potent, and centrally active antagonist of the tachykinin NK_1 receptor”))
- SCH388714 (developed by Schering-Plough) (Ex. 2063 at 3898 (showed “excellent selectivity,” “good oral bioavailability,” and it displayed “very good brain penetration” in animals))
- Rolapitant (developed by Schering-Plough) (Ex. 2051 at 9)
- TAK637 (developed by Takeda) (Ex. 2061 at 980 (“found effective after oral administration”))
- HSP117 (developed by Hisamitsu) (Ex. 2056 at 169 (“inhibitory activity of HSP-117 being about 50-fold that of CP-99,994 . . . [and] significantly inhibited retching and vomiting induced by copper sulphate and morphine . . . .” The results indicate that “HSP-117 is a potent anti-emetic agent, blocking NK-1 receptors in the nucleus tractus solitarius”))
- KRP-103 (developed by Kyorin Pharm) (Ex. 2064)
- SLV317 (developed by Solvay) (Ex. 2065 at 414 (“orally active and highly effective antagonist of substance P-induced effects in human”))

(*See also* Ex. 1002 at 3:23-42; Ex. 2057 at 1661 (Table 4); Ex. 2051 at 9; *see also* Ex. 2061.) Dr. Peroutka failed to consider any of these compounds as part of his analysis.

219. Notably, despite this long list of NK-1 receptor antagonists investigated, the only active pharmaceutical ingredients approved today in the NK-1 receptor antagonist class are aprepitant, netupitant, and rolapitant.[30] In a 2004 publication, Dr. Malcom MacCoss (the scientist who led the discovery of aprepitant) recognized that "it is very likely that tens of thousands of [NK-1 receptor antagonist] molecules have been prepared in the past decade as substance P antagonists, a large percentage of which likely exhibited sub-nanomolar potency at the NK-1 receptor, but only one has made it to market. This example highlights the difficulty and resources needed to optimize the ancillary properties of potent

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[30] Rolapitant was first marketed as an oral CINV treatment drug, and then its manufacturer developed an IV formulation of rolapitant. But following FDA approval of IV rolapitant, its manufacturer announced its withdrawal from U.S. distribution due to hypersensitivity reactions, including anaphylaxis and anaphylactic shock, which may occur during or following administration. (*See, e.g.*, Ex. 2080 at 5.)

inhibitors/antagonists so that they can become safe, viable medicines." (Ex. 2096 at 1812-13.)

220. A POSA would have known that a very large number of NK-1 receptor antagonists were under investigation by November 2009. At that time, only aprepitant had been FDA-approved and marketed, and only one other NK-1 receptor antagonist (casopitant) had progressed to Phase III clinical trials. (Ex. 1010 at 146.) A POSA focused on using a different NK-1 receptor antagonist than aprepitant would have been aware of the "remarkable number of small molecule NK_1 receptor antagonists" identified by many pharmaceutical companies in the last decade. (Ex. 1011 at 1362.)

D. Dr. Peroutka Fails to Show that a POSA Would Have Reasonably Expected that Substituting Netupitant for Aprepitant in Triple Therapy Would Have Successfully Improved Nausea Control

221. 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 NK_1 receptor antagonist (aprepitant) would work in the same manner to achieve similar (or improved) outcome." (*See, e.g.*, Ex. 1009 at ¶ 999.) I disagree with Dr. Peroutka's opinion.

222. By way of background, and as discussed above in Section VII, I understand that each independent claim of the '357 patent requires that the claimed

method treat CINV to a statistically significant degree compared to a baseline. Dependent claims 34, 35, 47, 48, 58, and 59 further require that the claimed regimen prevent and/or reduce the severity of nausea to a statistically significant degree, compared to a baseline. Dr. Peroutka has not explained why a POSA would have believed that replacing aprepitant (*see* Section VI.A), an NK-1 receptor antagonist that did not treat nausea, in triple therapy with a drug of the same class, like netupitant, would result in a treatment regimen that achieves these effects.

1. Dr. Peroutka's Reliance on Aprepitant Data Is Insufficient

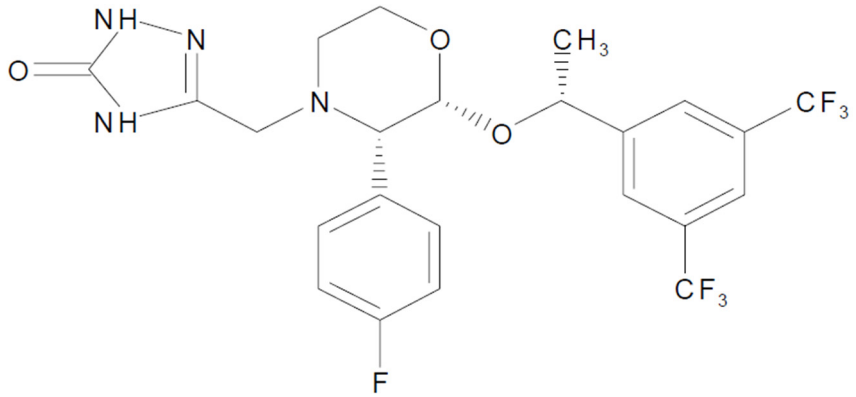
223. Dr. Peroutka has not provided any evidence that shows that a POSA could reasonably expect that a netupitant-based regimen that resulted from replacing aprepitant with netupitant in the gold-standard triple therapy would have provided an improved treatment for both nausea and vomiting as compared to standard therapy. (*See, e.g.,* Ex. 1009 at ¶¶ 999-1002.) Nor does he provide evidence that the netupitant-based regimen would have been expected to treat, prevent, or reduce the severity of nausea or vomiting. None of his cited references (Bös) discuss netupitant's effect on nausea and vomiting in humans.

224. In my opinion, a POSA would not be able to conclude, based on only aprepitant data, whether netupitant would be more effective in the treatment of nausea, including delayed nausea. Dr. Peroutka's cited reference, Bös, does not compare, for example, the potency, antagonism, selectivity, or CNS penetration

capabilities of aprepitant and netupitant. Dr. Peroutka's cited reference, Bös, also does not include any data comparing how aprepitant and netupitant interact with the NK-1 receptor, nor the effects that may arise from those compounds interacting with the NK-1 receptors. Dr. Peroutka notes that Bös teaches a dosing range of about 10 to 1,000 mg for a therapeutically effective dose. (Ex. 1009 at ¶ 882.) However, a POSA's ability to determine a dose for a given NK-1 receptor antagonist is irrelevant because Bös does not include nausea as one of the identified potential uses (*see* Section VI.B.3). And if a drug does not treat a patient (or even makes a condition worse), no dose adjustment could rectify that issue.

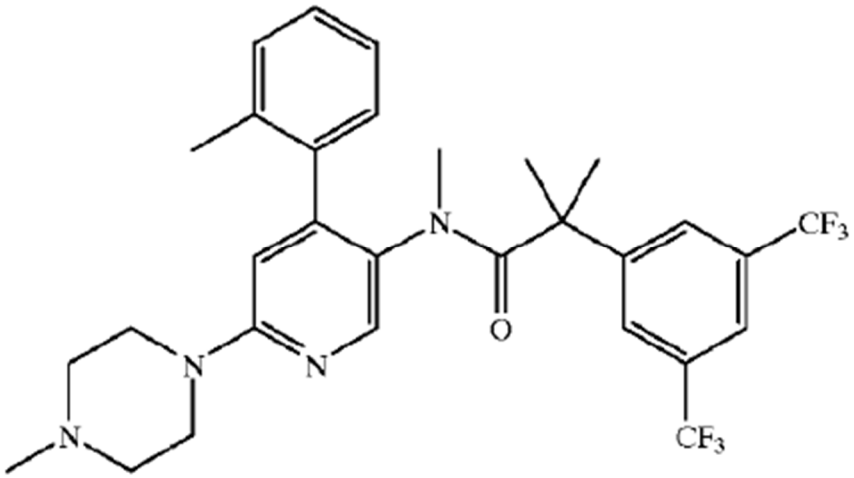
225. For example, a POSA would understand that aprepitant and netupitant have different chemical structures:

<u>Aprepitant</u>:



(Ex. 2016 at 1.)

Netupitant:



(Ex. 1014 at 14:9-30.) Given their differences in chemical structure, a POSA would expect that aprepitant and netupitant could engage the NK-1 receptor differently, potentially leading to differences in efficacy in treating a given condition. Accordingly, a POSA would have no reason to expect that just because one NK-1 receptor antagonist (*e.g.*, aprepitant) had a certain effect on nausea and vomiting, another NK-1 receptor antagonist (*e.g.*, netupitant) would achieve similar or improved outcomes. In my opinion, a POSA would be especially skeptical here given, as discussed further below in Section VIII.D.2, the high failure rate among NK-1 receptor antagonists.

a. Hargreaves Does Not Support Dr. Peroutka's Arguments

226. In my opinion, Dr. Peroutka seems to misunderstand the disclosures in Hargreaves and offers three conclusory opinions regarding reasonable expectation

of success that appear to be based on his improper assumption that aprepitant and netupitant would have a similar dose-receptor occupancy relationship. First, Dr. Peroutka opines that "[t]he POSA would have had a reasonable expectation of success in evaluating therapeutic efficacy of netupitant by applying PET NK_1 receptor occupancy as described in Hargreaves." (*See, e.g.*, Ex. 1009 at ¶ 1122.) As I explained above Section VI.B.2, dose-receptor occupancy relationships are drug-specific and not applicable to the drug class as a whole. This key distinction is why the '357 patent conducted a Netupitant PET Receptor Occupancy Study rather than relying solely on the information provided in Hargreaves regarding aprepitant receptor occupancy. (Ex. 1002 at Example 4.)

227. To the extent that Dr. Peroutka's opinion is that a POSA would have reasonably expected to succeed in evaluating whether a dose of netupitant would have been therapeutically effective based on aprepitant's dosing, plasma concentration, or NK-1 receptor occupancy, I disagree. In November 2009, netupitant's PK/PD information was largely unknown, and a POSA would have had no way of knowing, for instance, whether administering 125 mg of netupitant would alleviate emesis or cause serotonin syndrome. To the contrary, a POSA would know that they would need to replicate the Hargreaves study using netupitant-specific and dose-specific information to have any understanding of how to effectively dose netupitant to treat nausea and vomiting.

228. Second, Dr. Peroutka opines that "Hargreaves teaches that a therapeutically effective amount of NK_1 receptor antagonist occupies at least about 75% of NK_1 receptors in the striatum." (*See, e.g.*, Ex. 1009 at ¶ 1130.) I disagree with Dr. Peroutka's opinion. At best, Hargreaves teaches a POSA that, to potentially be therapeutically effective in some capacity, a specific dose of aprepitant must occupy at least about 90% of NK_1 receptors in the striatum. Hargreaves disclosed that "[i]n the treatment of patients who developed CINV in response to treatment with cisplatin, ***an initial daily dose of 40 mg of aprepitant*** followed by 25-mg daily doses ***showed some efficacy, but*** a higher dosing regimen (***initial dose of 125 mg***, followed by subsequent daily doses of 80 mg) ***was considerably more effective***." (*See* Ex. 1012 at 23.) Next, Hargreaves disclosed "[n]o further efficacy improvements over the 125-mg/80-mg aprepitant regimen were observed with the highest dose (initial dose of 375 mg, followed by 125-mg daily dose)." (Ex. 1012 at 23.) Therefore, a POSA would have understood that, if aprepitant's dose-response relationship somehow applied to all NK-1 receptor antagonists, the dose of the NK-1 receptor antagonist needed to for consistent clinical benefits must achieve an NK-1 receptor occupancy of ≥ 90%, and multiple doses would be needed to achieve this level of receptor occupancy over a multi-day time period. (*See* Ex. 1012 at 23-24.)

229. Dr. Peroutka's opinion that the NK-1 receptor antagonist only needs to occupy about 75% of NK-1 receptors in the striatum relies on the initial dose of 40 mg of aprepitant which merely **showed some efficacy in reducing emesis**. (*See* Ex. 1012 at 23.) A POSA would understand that the goal of a therapeutically effective amount of netupitant is to provide patients with consistent clinical benefits in the treatment of CINV, not show "some efficacy" in that treatment.

230. Lastly, Dr. Peroutka opines that "Hargreaves describes that there is a direct relationship between NK_1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness for patients suffering from chemotherapy-induced nausea and vomiting." (Ex. 1009 at ¶ 1131.) Again, I disagree. As I explained above, Section VI.B.2, dose-receptor occupancy relationships are drug-specific, not applicable to an entire drug class or receptor type. Furthermore, there simply is not a "direct relationship" between NK-1 receptor occupancy in the striatum and antiemetic therapeutic effectiveness, but rather a complex association involving various drug-specific and dose-dependent PK and PD properties, including but not limited to degree and duration of receptor occupancy, relationship between blood concentration, response, and time, and drug clearance.

231. On top of that, as I explained above in Sections V.B.4 and VI.B.1, the undefined pathophysiology of all the conditions and drugs involved, as well as the high failure rate of NK-1 receptor antagonists in general, underscore the extremely

high level of unpredictability to a POSA in the field of drug development. The relationship between dose, plasma concentration, and NK-1 receptor occupancy for netupitant were unknown in November 2009.

232. Dr. Peroutka seemingly attempts to use the disclosure of Bös to cure the deficiencies of Hargreaves disclosure, opining that "seventy-two (and ninety-six) hours is squarely within the therapeutic period and reflects the known prolonged half-life of netupitant." (Ex. 1009 at ¶ 1132.) But these references do not mention anywhere that netupitant has a 72 or 96 hour half-life in humans. In fact, Bös provides three different half-lives in animals only, and none of these are 72 or 96 hours: (1) 30 hours in gerbils, (2) 24 hours in rats, and (3) 18 hours in dogs. (Ex. 1014 at 19:07-37.) Dr. Peroutka has not explained how a POSA would have extrapolated these half-lives to humans. Hargreaves supplies no information about netupitant at all, let alone its half-life in humans.

233. Moreover, netupitant's half-life does not directly translate to receptor occupancy, which instead is determined by many of netupitant's pharmacokinetic and pharmacodynamic properties. Importantly, Dr. Peroutka does not (and cannot) point to any prior art that discloses the amount of netupitant that would result in the specific claimed level of receptor occupancy over the specific claimed timeframe. (*See, e.g.*, Ex. 1009 at ¶ 1116 (citing Ex. 1002 at 4:37-51).) Similarly, Bös does not disclose what amount of netupitant would be for treating, preventing, or

reducing the severity of nausea and vomiting in a human in need thereof, nor a dose of netupitant that would occupy at least 70% of the NK-1 receptors in the striatum of a human for 72 or 96 hours.

2. Dr. Peroutka Did Not Consider the High Failure Rate of NK-1 Receptor Antagonists

234. As discussed above, and in my opinion, a POSA would have known that a large number of NK-1 receptor antagonists had been investigated by November 2009. (*See* Section VI.B.1, VIII.C.2.) However, by November 2009, only one NK-1 receptor antagonist (aprepitant) was approved by the FDA for use as an active pharmaceutical ingredient. (*See, e.g.*, Ex. 1010 at 143.)

235. At his deposition, Dr. Peroutka estimated that the probability of success for any NK-1 receptor antagonist that had CNS entry and some preclinical data in animal models would be about "80-plus" percent. (*See* Ex. 2086 at 87:21-90:6.) In my opinion, Dr. Peroutka fails to appreciate that many NK-1 receptor antagonists that were investigated failed to show safety and efficacy, and ultimately, did not receive FDA approval. (*See* Section VI.B.1, VIII.C.2; *see also* Ex. 2096.)

236. Dr. Peroutka's speculation that any NK-1 receptor antagonist with good preclinical data could ultimately be successful and approved by the FDA is unsupported. Dr. Peroutka also testified that no NK-1 receptor antagonist failed

prior to November 2009. (*See* Ex. 2086 at 89:17-90:12.) His testimony, however, ignores the failure of casopitant, which was publicly known by September 2009. (*See* Section VI.B.1; Ex. 2077; Ex. 1036.)

3. Dr. Peroutka Fails to Show that There was an Expectation that a Single Dose of Netupitant would Prevent or Reduce the Severity of Nausea

237. As discussed above, Section VIII.D, Dr. Pertouka's reliance on aprepitant data to assert that netupitant, a different NK-1 receptor antagonist, would treat nausea, is insufficient. Dr. Peroutka relies on Herrington for clinical studies with a single dose of aprepitant. (*See, e.g.*, Ex. 1009 at ¶¶ 1009-10, 1059-60.) However, as discussed above, Section VI.A.4, Herrington did not show a single dose of aprepitant with palonosetron and dexamethasone treats nausea to a statistically significant degree compared to a baseline of palonosetron and dexamethasone. (*See* Section VI.A.4.) Dr. Peroutka does not explain why a POSA would expect a single dose of netupitant to prevent or reduce the severity of nausea when a single dose of aprepitant failed to prevent or reduce the severity of nausea.

IX. OBJECTIVE INDICIA

238. I understand from counsel that certain evidence (referred to as "objective indicia") was relevant to Dr. Peroutka's opinions. This evidence

includes facts pertaining to unexpected results and skepticism, among others. I discuss them below.

A. Nexus

239. As discussed above in Section VII, the claims of the ’357 patent claim a netupitant-palonosetron-based regimen that is able to treat both nausea and vomiting, in particular delayed nausea, in patients undergoing chemotherapy to a degree of statistical significance compared to baseline. This unique ability of the combination of netupitant and palonosetron to treat nausea following chemotherapy is an important innovation for patients living with cancer, as delayed nausea is considered one of the most debilitating side effects of chemotherapy. (*See* Section V.A.)

240. Example 5 of the ’357 patent specification demonstrates this unique feature of combining netupitant and palonosetron. (*See* Ex. 1002 at 16:61-19:44.) Example 5 describes a Phase 2 clinical trial that evaluated three different single doses of netupitant (100 mg, 200 mg, and 300 mg) combined with palonosetron and dexamethasone for treatment of nausea and vomiting following chemotherapy, as compared to palonosetron and dexamethasone. (Ex. 1002 at 16:61-17:3.) This Phase 2 clinical trial in human patients was a multicenter, randomized, double-blind study. (Ex. 1002 at 17:15-18.) Patients were randomized to one of the following treatment groups:

> Group 1—0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone standard regimen: 20 mg. on Day 1 and 8 mg. BID from Day 2 through Day 4)
> Group 2—100 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)
> Group 3—200 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with an oral dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)
> Group 4—300 mg. oral netupitant plus 0.5 mg. oral palonosetron on Day 1 (with dexamethasone adjusted regimen*: 12 mg. on Day 1 and 8 mg. daily from Day 2 to Day 4)
> Group 5—125 mg. oral aprepitant plus IV ondansetron 32 mg. (both on Day 1) then 80 mg. oral aprepitant on Day 2 and Day 3, (all with an oral dexamethasone adjusted regimen: 12 mg. on Day 1 and 8 mg. daily from Day 2 through Day 4)

(*Id.* at 17:15-64.) Group 1 served as the control group and received standard therapy, while Group 5 received the regimen in the Emend® Label of dexamethasone, ondansetron, and aprepitant. (*See id.*) Groups 2, 3, and 4 received dexamethasone, palonosetron, and netupitant (in doses of 100 mg, 200 mg, and 300 mg of netupitant, respectively). (*See id.*)

241. The objective of this study was to compare the efficacy and safety of three single oral doses of netupitant when combined with palonosetron and dexamethasone, versus standard therapy of palonosetron and dexamethasone alone, for the prevention of chemotherapy-induced nausea and chemotherapy-induced vomiting in patients receiving highly emetogenic chemotherapy. (*Id.* at 17:4-9.)

Notably, Example 5 provides a proper baseline comparison (Group 1) to determine the effect of adding netupitant to standard therapy. (*Id.* at 17:15-64.) In addition, Group 5, which received the FDA-approved oral aprepitant regimen with ondansetron and dexamethasone, was included as "an active comparator for exploratory purposes." (*Id.* at 17:9-12.)

242. The primary efficacy endpoint was "complete response" within 120 hours after the start of highly emetogenic chemotherapy. Secondary endpoints included the following:

> Complete response for the 0-24 hour interval (acute phase); and for the 25-120 hour interval (delayed phase);
> Complete protection (defined as no emesis, no rescue therapy, no significant nausea); Total control (defined as no emesis, no rescue therapy and no nausea); No nausea (maximum VAS<5 mm); No significant nausea (maximum VAS<25 mm); No rescue medication; No emesis. These endpoints were evaluated for the 0-120 hour interval (overall), acute and delayed phase.
> Time to first emetic episode, Time to first rescue medication, Time to treatment failure (based on time to the first emetic episode or time to the first rescue medication, whichever occurs first);
> Severity of nausea for the overall, acute and delayed phase; Patient global satisfaction with anti-emetic therapy by means of VAS for each 24 hour interval.

(Ex. 1002 at 18:4-24.)

243. Table 6 summarizes the results for the main secondary endpoints:

TABLE 6

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

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Emesis						
Overall	76.5	87.4*	87.6*	91.1*	87.3*	
Acute	89.7	93.3	92.7	98.5*	94.8	
Delayed	80.1	90.4*	91.2*	91.9*	89.6*	
No 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. 1002 at 19:1-43 (Table 6).) As shown in Table 6, the 300 mg dose of netupitant, when administered with palonosetron and dexamethasone, showed a statistically significant improvement as compared to standard therapy on (1) no emesis in the overall, acute, and delayed phases, (2) no nausea in the delayed phase, and (3) no significant nausea in the overall, acute, and delayed phases. (*Id.*)

244. The data in Example 5 demonstrates how to administer netupitant and palonosetron to the patient in therapeutically effective amounts that will make a clinically meaningful difference in the patient's nausea. (Ex. 1002 at Example 5.) As discussed further below in Section IX.B, Table 6 shows that a single dose of 300 mg netupitant, a single dose of 0.5 mg palonosetron, and dexamethasone (12 mg on day 1, and 8 mg on day 2) are associated with statistically significant and clinically meaningful effects on both nausea and vomiting. I note that the dose of dexamethasone (12 mg) is considered a "subtherapeutic" dose, which would be ineffective against chemotherapy-induced nausea and vomiting when administered alone, but is effective when administered in combination with netupitant. (Ex. 1002 at Example 5.)

245. These beneficial, novel effects of a netupitant-based triple therapy regimen that also includes palonosetron and dexamethasone result from following the method in the various challenged claims of the '357 patent. These effects include the ability to treat both nausea and vomiting in a manner that is both statistically and clinically meaningful compared to standard therapy.

B. Unexpected Results and Skepticism

246. Dr. Peroutka opines that a POSA would have understood that the data sets provided in Table 6 of Example 5 of the '357 patent specification "illustrates 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 identifies no data that shows aprepitant had a statistically significant improvement in the control of nausea following chemotherapy. (*See* Section VI.A.) As I explain in detail below, the combination of palonosetron and netupitant achieved what aprepitant, in combination with other drugs (with or without palonosetron), failed to do.

247. In particular, the claimed netupitant regimen unexpectedly demonstrated a statistically significant and clinically meaningful result on "no nausea" during the delayed phase, which is the most debilitating and hardest to treat.[31] As discussed in the section immediately above, Table 6 of the '826 patent

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[31] Today, the claimed netupitant-palonosetron regimen in a single dose is viewed as promising for controlling nausea at an even later time point (> 120 hours), which is described as "late onset nausea." (*See* Ex. 2100 at 1261.) This type of nausea may occur in connection with certain emerging treatment options (*e.g.*, antibody-drug conjugates) that have effects that can last for an extended duration. (*See* Ex. 2100 at 1261, 1268.) In contrast to netupitant-palonosetron, a single dose of aprepitant-palonosetron is unable to control nausea at > 120 hours, a

specification demonstrates netupitant in combination with palonosetron and dexamethasone showed a statistically significant effect in improving control of nausea (green highlights), compared to standard therapy (yellow highlights):

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. 1002 at Table 6.) In contrast, aprepitant-based triple therapy administered to patients in Group 5 did not show a statistically significant improvement in

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clinical outcome which underscores the pharmacological difference in half-life and NK-1 receptor occupancy between netupitant and aprepitant. (*See* Ex. 2100 at 1268.)

"no nausea" or "no significant nausea" (pink highlights) compared to standard therapy.[32] I note that the aprepitant-based triple therapy used the same components as the clinical trials in MASCC and Herrstedt. (*See* Section VI.A.)

248. As discussed further above in Section VI.A, a POSA at the relevant time would have been skeptical that another NK-1 receptor antagonist would work for nausea, because the available scientific literature hypothesized that nausea may be associated with unique neuroreceptors that were not targeted by NK-1 receptor antagonists.

249. For example, the available literature observed that:

- "The more pronounced effect of aprepitant and 5-HT_3-receptor antagonists on the prevention of vomiting compared with nausea implies that serotonin and substance P may play a relatively more important role in the

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[32] To the extent, Dr. Peroutka asserts aprepitant-based triple therapy needs to be compared using palonosetron as the 5-HT_3 receptor antagonist in the regimen, Herrington (Ex. 1016) concluded that "the severity of nausea was not different" when triple therapy of dexamethasone-palonosetron-aprepitant was compared to standard therapy of dexamethasone-palonosetron (Ex. 1016 at 2084; *see also* Section VI.A.5.)

pathogenesis of vomiting than of nausea, and that other neurotransmitters may also be involved in the pathogenesis of these symptoms, especially nausea." Ex. 1034 at 2829;

- Aprepitant-based triple therapy drug regimen nausea results are not significantly different than the standard therapy control group "suggest[ing] that the neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting." Ex. 2073 at 1005;
- "Although the efficacy of aprepitant-based anti-emetic regimen was similar to standard regimens, 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. This confirms that the agent is active against vomiting induced by serotonin and substance P, while nausea is possibly related to some other neurotransmitters for which aprepitant has limited efficacy." Ex. 1048 at 548.

250. These observations from the relevant literature are consistent with my opinions discussed above in Section VI.A about how the prior art showed aprepitant was not effective against nausea. At the relevant time, a POSA would have understood that, because aprepitant showed no improvement in the treatment

of nausea as compared to standard therapy, nausea must be associated with unique neuroreceptors that were not targeted by NK-1 receptor antagonists.

251. In the face of this skepticism, the inventor's discovery that netupitant could, in fact, provide an improved treatment for nausea when combined with palonosetron was unexpected and very surprising. As a potential explanation for these unexpected results, the inventors began hypothesizing why the "unanticipated statistically significant effect against nausea . . . [had] not previously been observed in clinical studies" (Ex. 1005 at 345, ¶ 28) of other NK-1 receptor antagonists in combination with other 5-HT_3 receptor antagonists. The inventors posited that this unexpected effect could be because co-administration of netupitant and palonosetron produces unexpected synergistic effects "result[ing] in even greater efficacy against nausea." (Ex. 1002 at 4:65-5:12.)

252. During prosecution of the first patent in the family, U.S. Patent No. 8,623,826 patent, Helsinn submitted a Rule 132 declaration explaining the unexpected synergistic effects of the netupitant-palonosetron combination in inhibiting substance P response.[33] (*See* Ex. 1005 at 334-338 (Helsinn's Remarks

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[33] 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.)

on synergistic effects, citing the Rule 132 declaration).) The Rule 132 declaration explained that the synergistic effects of this combination of palonosetron and netupitant on substance P ***inhibition*** was greater than the additive effects of netupitant and palonosetron when administered separately.

253. The Rule 132 declaration provided the following table describing the EC_{50} value of substance P in several experiments performed by Helsinn[34]:

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; *see also* Ex. 2101 at 27 (Table 1).)

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

254. 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 response. (*See* 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. (*See* Ex. 1005 at 343, ¶ 18.) Similarly, palonosetron at a concentration of 0.2 nM had no effect on substance P response. (*See* 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. (*See* Ex. 1005 at 343, ¶ 19.)

255. But when the inventors combined netupitant and palonosetron, even at concentrations where neither compound alone increased the EC_{50} of substance P, 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.[35] (*See* Ex. 1005 at 343, ¶ 21.) Additionally, when 30 nM netupitant and 2 nM palonosetron were combined, the concentration increased nearly ***500-fold*** to 970 µM. (*See* Ex. 1005 at 343, ¶¶ 22-23.) This exponential increase was very 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)." (*See* Ex. 1005 at 343, ¶¶ 22-23.) In other words, the synergistic effects of this innovative combination are substantially greater than the additive effects of netupitant and palonosetron when administered separately.

X. CONCLUSION

256. 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.

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[35] 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.

Dated: February 25, 2026 By: _____

Eric J. Roeland, M.D.

APPENDIX A

Exhibit No.	Description
1001	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 8,623,826 B2, issued 17 January 2014
1002	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,186,357 B2, issued 17 November 2015
1003	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 9,943,515 B2, issued 17 April 2018
1004	F. Trento et al., *Compositions and methods for treating centrally mediated nausea and vomiting*, U.S. Patent 10,828,297 B2, issued 10 November 2020
1005	Prosecution history for U.S. Appl. 13/077,462, filed 31 March 2011
1006	Prosecution history for U.S. Appl. 14/069,927, filed 01 November 2013
1007	Prosecution history for U.S. Appl. 15/003,327, filed 19 May 2016
1008	Prosecution history for U.S. Appl. 15/923,050, filed 16 March 2018
1009	Expert Report of Dr. Peroutka (Ex. 1009)
1010	J. Herrstedt & P. Dombernowsky, *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 Basic & Clinical Pharmacology & Toxicology 143-150 (2007)
1011	T. Hoffmann et al., *Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists*, 16 Bioorganic & Medicinal Chemistry Letters 1362-1365 (2006)

Exhibit No.	Description
1012	R. Hargreaves, *Imaging Substance P Receptors (NK1) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. Clinical Psychiatry 18-24 (2002)
1013	The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), *Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference*, 17 Annals of Oncology 20-28 (2006)
1014	M. Bös et al., *4-phenyl-pyridine derivatives*, U.S. Patent 6,297,375 B1 (issued 2 Oct. 2001)
1015	Eisai, Inc., ALOXI (palonosetron HCl) Capsules, package insert (Aug. 2008)
1016	J.D. Herrington et al., *Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting*, 112 Cancer 2080 (2008).
1017	D. Bonadeo et al., *Soft Capsules Comprising Palonosetron Hydrochloride Having Improved Stability and Bioavailability*, PCT Publication WO 2008/049552 (published 2 May 2008)
1019	K. Jordan et al., *Guidelines for Antiemetic Treatment of Chemotherapy-Induced Nausea and Vomiting: Past, Present, and Future Recommendations*, 12 The Oncologist 1143-1150 (September 2007)
1020	Curriculum Vitae of Dr. Stephen J. Peroutka
1022	M.S. Aapro et al., *A phase III, double-blind, randomized trial of palonosetron compared with ondansetron in preventing chemotherapy-induced nausea and vomiting following highly emetogenic chemotherapy*, 17 Annals of Oncology 1441-49 (2006)

Exhibit No.	Description
1023	D. Campos et al., *Prevention of cisplatin-induced emesis by the oral neurokinin-1 antagonist, MK-869, in combination with granisetron and dexamethasone or with dexamethasone alone*, 19(6) Journal of Clinical Oncology, 1759 (2001)
1030	Merck & Co., EMEND, package insert (2008)
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