Petitioner Azurity's Demonstratives

Azurity Pharmaceuticals, Inc. v. Helsinn Healthcare S.A.

IPR2025-00945, IPR2025-00946,

IPR2025-00947, IPR2025-00948, & IPR2025-00949

U.S. Patent Nos. 8,623,826, 9,186,357,

9,943,515, & 10,828,297

Grounds – IPR2025-00945 (US 8,623,826)

Ground	Claims	Basis
1	19, 22-23, 25	§103: MASCC, Hoffmann
2	19-20, 22-23, 25	§103: MASCC, Bös
3	19-23, 25	§103: MASCC, Bös, ALOXI
4	1-3, 8-10, 15-18, 24	§103: Herrstedt, Hoffman, Hargreaves
5	1-3, 8-10, 15-18, 24	§103: Herrstedt, Bös, Hargreaves
6	4-5	§103: Herrstedt, Bös, Hargreaves, Herrington
7	10-14	§103: Herrstedt, Bös, Hargreaves, ALOXI

Grounds – IPR2025-00946 (US 9,186,357)

Ground	Claims	Basis
1	2-4, 11-16, 40, 52-54, 56–62	§103: Herrstedt, Bös
2	41-42	§103: Herrstedt, Bös, Herrington
3	55	§103: Herrstedt, Bös, Hargreaves

Grounds – IPR2025-00947 (US 9,186,357)

Ground	Claims	Basis
1	1, 5-10, 17	§103: Herrstedt, Bös
2	18, 19, 25-27, 30-32	§103: Herrstedt, Bös, Herrington
3	20	§103: Herrstedt, Bös, Herrington, ALOXI
4	24, 29	§103: Herrstedt, Bös, Hargreaves, Herrington
5	28	§103: Herrstedt, Bös, Bonadeo, Herrington
6	21-23, 33-35, 38-39, 43-44, 46-51	§103: Herrstedt, Bös, Bonadeo, Herrington, ALOXI
7	36, 45	§103: Herrstedt, Bös, Bonadeo, Hargreaves, Herrington, ALOXI

Grounds – IPR2025-00948 (US 9,943,515)

Ground	Claims	Basis
1	11-17, 19-23	§103: Herrstedt, Bös, Herrington
2	1-10, 18	§103: Herrstedt, Bös, Hargreaves, Herrington

Grounds – IPR2025-00949 (US 10,828,297)

Ground	Claims	Basis
1	1-4, 8-13, 17-19, 23	§103: Herrstedt, Bös
2	5, 6, 14, 15, 20, 21	§103: Herrstedt, Bös, ALOXI
3	7, 16, 22	§103: Herrstedt, Bös, Hargreaves

Established Standard of Care for CINV

- By November 2009, the standard of care for treatment of chemotherapy-induced nausea and vomiting (CINV) was a three-drug antiemetic regimen:
  - NK1 antagonist
  - 5-HT3 antagonist
  - dexamethasone
- MASCC (EX1013) and Herrstedt (EX1010) each supply this standard of care:

MASCC:

> Previous recommendations suggest a combination of a 5-HT3-receptor antagonist plus dexamethasone as the regimen of choice for the prevention of acute emesis in cisplatin-treated patients [1, 2].
>
> Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT3-receptor antagonist plus dexamethasone [4].

Herrstedt:

> Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy [37–39] or a combination of cyclophosphamide plus an anthracycline [40]. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 postcisplatin', was the primary end-point in all studies. Two of the HEC studies [37,38] used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2–4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2–4 plus aprepitant days 2–3. In the Hesketh

EX1017, 11-12, 16

Grounds References: MASCC (EX1013)
Triple-Therapy Standard of Care for CINV

review

Annals of Oncology 17: 20–28, 2006
doi:10.1093/annonc/mdj078
Published online 28 November 2005

Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference

The Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC)†

Medical Oncology Division, Silvestrini Hospital, Perugia, Italy

Received 6 October 2005; accepted 17 October 2005

review

Background: In the late 1990s, several professional organizations convened antiemetic guideline groups and published the findings of these expert panels. Each of these documents was based on analyses of the available published trials and provided nearly similar recommendations. Nonetheless, small differences in emetic risk categories and treatment recommendations led to confusion in antiemetics selection. With the emergence of new findings and agents since the guidelines were initially published, many of the oncology professional societies have updated the antiemetic guidelines.
Materials and methods: A literature review up to March 2004 was carried out using MEDLINE with evaluation of the evidence by an expert panel composed of 23 oncology professionals in clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology. The experts represented nine oncology professional societies and came from 11 different countries on four continents.
Results: Recommendations on antiemetic regimens to prevent emesis induced by high, moderate, low and minimal risk chemotherapy were suggested as well as management of anticipatory emesis. Furthermore, recommendations for refractory emesis, emesis induced by high-dose chemotherapy and radiotherapy and for antiemetics in children receiving chemotherapy were elaborated.
Conclusions: Recommendations about antiemetic prophylaxis in patients receiving treatment with chemo- and radiotherapy have been updated by representatives of nine oncological organizations.
Key words: acute emesis, aprepitant, delayed emesis, dexamethasone, 5-HT3-receptor antagonists, metoclopramide

introduction

Despite progress in the last 20 years, vomiting and nausea continue to be significant side effects of cancer therapy. In the late 1990s, to define the optimal antiemetic prophylaxis in patients receiving treatment with chemotherapy and radiotherapy, several professional organizations convened guideline groups and published the finding of these expert panels. Each of these documents was based on analyses of the published trials and on the whole provided similar recommendations. Nevertheless, small differences in the number of emetic risk categories and in some treatment recommendations confused many individuals attempting to implement the guidelines.

With the emergence of new research findings and agents since the most recent guidelines, many of the oncology professional societies have encouraged an update of the antiemetic guidelines. Therefore, in 2004 a new guideline process was initiated and conducted by representatives from nine oncology organizations: the American Society of Clinical Oncology (ASCO), Cancer Care Ontario (CCO), the Clinical Oncology Society of Australia (COSA), the European Oncology Nursing Society (EONS), the European Society of Medical Oncology (ESMO), the Multinational Association of Supportive Care in Cancer (MASCC), the National Comprehensive Cancer Network (NCCN), the Oncology Nursing Society (ONS) and the South African Society of Medical Oncology (SASMO). The MASCC served as the host organization.

The methodology for this guideline process was based on a literature review up to March 2004 using MEDLINE (National Library of Medicine, Bethesda, MD, USA) and other databases, with evaluation of the evidence by an expert panel composed of 23 oncology professionals in clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology. The experts represented the nine oncology

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Azurity Pharmaceuticals, Inc. EXHIBIT - 1013

Previous recommendations suggest a combination of a 5-HT3-receptor antagonist plus dexamethasone as the regimen of choice for the prevention of acute emesis in cisplatin-treated patients [1, 2].

Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT3-receptor antagonist plus dexamethasone [4].

Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists. Two studies in patients treated with chemotherapy of moderate emetic risk demonstrated efficacy with a single intravenous dose of palonosetron 0.25 mg that was equal or better to a single intravenous dose of dolasetron or ondansetron in both the acute and delayed phases [20, 21]. In neither study were corticosteroids used. Somewhat surprisingly, a higher dose of palonosetron was less effective than a lower dose although still numerically superior to the comparator 5-HT3-receptor antagonist.

EX1013, 22, 24

Grounds References: Herrstedt (EX1010)
Triple-Therapy Standard of Care for CINV

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MiniReview

Anti-Emetic Therapy in Cancer Chemotherapy: Current Status

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(Received March 26, 2007; Accepted June 19, 2007)

Abstract: Nausea and vomiting are ranked as the most severe side effects to chemotherapy by cancer patients. Twenty years ago, treatment of nausea and vomiting from chemotherapy only had moderate effect and often unpleasant side effects. The drugs used included dopamine$_2$-receptor antagonists and corticosteroids alone or combined. This review summarizes the development of anti-emetic therapy, but will focus on the importance of two new classes of anti-emetics: the serotonin$_3$- and the neurokinin$_1$-receptor antagonists. Furthermore, evidence-based guidelines for the treatment of chemotherapy-induced nausea and vomiting will be given. The serotonin$_3$-receptor antagonists, the first group of drugs developed specifically as anti-emetics, have significantly improved the prophylaxis of chemotherapy-induced emesis especially in combination with a corticosteroid. The improvement in the prophylaxis of nausea with this combination is however modest. A new group of anti-emetics, the neurokinin$_1$-receptor antagonists, has now been developed, and the first drug, aprepitant, was marketed in 2003. Aprepitant 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. The importance of drug–drug interactions with anti-emetics and other drugs, especially cytotoxins, through their competition for cytochrome P450 enzymes, have been studied. At present, there is no evidence that such interactions are of major clinical importance. Evidence-based clinical guidelines are now available and regularly updated, but unfortunately clinical implementation is slow. Recommendations for some types of chemotherapy-induced emesis such as delayed emesis, is based on a low level of evidence. Furthermore, the majority of clinical trials include highly selected groups of patients not permitting definite conclusions for other and more heterogeneous patient groups. Development of new anti-emetics with other mechanisms of action is awaited with interest.

Nausea and vomiting are ranked by patients as two of the worst adverse effects of cancer chemotherapy [1]. Twenty-five years ago, nausea and vomiting were inevitable adverse effects of cancer chemotherapy, but the development of new and potent anti-emetics has led to a significant decrease in a number of patients suffering from chemotherapy-induced vomiting. Today, the majority of patients consider nausea as the main problem.

Chemotherapy-induced nausea and vomiting is divided in the acute and the delayed phase, occurring 0–24 hr and 24–120 hr after initiation of chemotherapy. Furthermore, some patients suffer from anticipatory nausea or vomiting in the last few days before chemotherapy, in particular those who have experienced nausea or vomiting during previous cycles of chemotherapy.

The risk of suffering from nausea and vomiting is dependent on the emetic potential of the chemotherapy, specific patient risk factors and on the anti-emetic treatment. Young age, female gender and vomiting during previous chemotherapy are the most potent risk factors, whereas large alcohol consumption seems to be protective. In table 1, the emetic potential of the most common cytotoxins are given. Patients receiving chemotherapy with a high emetic potential (more than 90% risk) or a moderate emetic potential (30–90% risk) have been most frequently investigated. It should be recognized that not only the specific cytotoxin but also the dose and the combination with other cytotoxins are risk factors.

This review summarizes the development of anti-emetic therapy, but will focus on the importance of two new classes of anti-emetics, the serotonin$_3$- and the neurokinin$_1$-receptor antagonists. Furthermore, evidence-based guidelines for the treatment of chemotherapy-induced nausea and vomiting will be given.

Pathophysiology

The emetic reflex protects human beings from poisoning by digestion of toxic substances. Therefore, emesis is a natural consequence of treatment with most cancer chemotherapy. The understanding of the emetic reflex arch is complicated and subject to current changes.

During the past 100 years, we have operated with terms as 'the vomiting centre' and the chemoreceptor trigger zone located in the lateral reticular formation and in the area postrema of the medulla oblongata, respectively [2,3]. The chemoreceptor trigger zone is located outside the blood-brain

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Azurity Pharmaceuticals, Inc. EXHIBIT - 1010

Abstract: Nausea and vomiting are ranked as the most severe side effects to chemotherapy by cancer patients. Twenty years ago, treatment of nausea and vomiting from chemotherapy only had moderate effect and often unpleasant side effects. The drugs used included dopamine$_2$-receptor antagonists and corticosteroids alone or combined. This review summarizes the development of anti-emetic therapy, but will focus on the importance of two new classes of anti-emetics: the serotonin$_3$- and the neurokinin$_1$-receptor antagonists. Furthermore, evidence-based guidelines for the treatment of chemotherapy-induced nausea and vomiting will be given. The serotonin$_3$-receptor antagonists, the first group of drugs developed specifically as anti-emetics, have significantly improved the prophylaxis of chemotherapy-induced emesis especially in combination with a corticosteroid. The improvement in the prophylaxis of nausea with this combination is however modest. A new group of anti-emetics, the neurokinin$_1$-receptor antagonists, has now been developed, and the first drug, aprepitant, was marketed in 2003. Aprepitant 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. The importance of drug–drug interactions with anti-emetics and other drugs, especially cytotoxins, through their competition for cytochrome P450 enzymes, have been studied. At present, there is no evidence that such interactions are of major clinical importance. Evidence-based clinical guidelines are now available and regularly updated, but unfortunately clinical implementation is slow. Recommendations for some types of chemotherapy-induced emesis such as delayed emesis, is based on a low level of evidence. Furthermore, the majority of clinical trials include highly selected groups of patients not permitting definite conclusions for other and more heterogeneous patient groups. Development of new anti-emetics with other mechanisms of action is awaited with interest.

Ondansetron, granisetron, tropisetron, dolasetron and palonosetron are marketed in the USA and a number of European and other countries, whereas ramosetron and azasetron are marketed in Japan only. Palonosetron, the newest of these agents, has a very potent and specific binding at 5-HT$_3$ receptors and a half-life around 40 hr as compared to less than 10 hr for the other agents (table 3).

Four phase III trials have investigated the use of aprepitant in patients receiving cisplatin-based, highly emetogenic chemotherapy [37–39] or a combination of cyclophosphamide plus an anthracycline [40]. Complete response, defined as 'no emesis and no rescue therapy on days 1–5 postcisplatin', was the primary end-point in all studies. Two of the HEC studies [37,38] used an identical design comparing ondansetron, dexamethasone and placebo day 1 followed by dexamethasone plus placebo days 2–4 with ondansetron, dexamethasone and aprepitant day 1 followed by dexamethasone days 2–4 plus aprepitant days 2–3. In the Hesketh study [37], a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen ($P < 0.001$), and in the Poli-Bigelli study [38] complete response rates were 62.7% versus 43.3% ($P < 0.001$). The most recently published HEC study [39] used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4. Again a statistically benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm ($P = 0.003$). In the first two studies, a difference of approxi-

EX1010, Abstract, 145-46

Grounds References: Hoffmann (EX1011)
Netupitant as Promising NK1 Receptor Antagonist

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Bioorganic & Medicinal Chemistry Letters 16 (2006) 1362–1365
Bioorganic & Medicinal Chemistry Letters

Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists

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Received 11 September 2005; revised 14 November 2005; accepted 14 November 2005
Available online 5 December 2005

Abstract—The discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK_1) receptor antagonists is described. The evaluation of this class is briefly outlined, leading to the identification of netupitant **21** and befetupitant **29**, two new proprietary chemical entities with high affinity and excellent CNS penetration.
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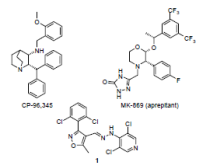
Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK_1, NK_2 and NK_3. The endogenous ligand for NK_1 receptors is the 11 amino acid neuropeptide substance P.[1] Following the discovery of the first non-peptide NK_1 receptor antagonist CP-96,345 in 1991,[2] a remarkable number of small molecule NK_1 receptor antagonists were identified by many pharmaceutical companies in the last decade.[3]



Moreover, recent clinical trials have demonstrated an important therapeutic application for NK_1 receptor antagonists in the control of cancer chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression.[4] MK-869 (aprepitant) was the first NK_1 receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.[5]

Following 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 (e.g., **1**, $K_i = 15$ nM). We hypothesized that **1** might be able to adopt conformations which are in agreement with the pharmacophore model described by researchers from Merck.[6] Moreover 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. Consequently, we decided to embark on the optimization of this compound class during a focused lead generation and optimization program.

During the initial steps of our optimization efforts, it was discovered that the 5-membered heterocyclic isoxazole backbone of **1** could be replaced by a simple isocyclic benzene core (**2a–e** Table 1). Subsequently the *N*-(4-pyridyl)-hydrazone substituent, which was associated with potential toxicity liabilities, was replaced by the

Keywords: NK_1 receptor antagonist; G-protein coupled receptor; Drug design and synthesis.
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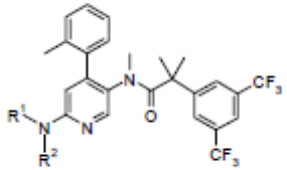
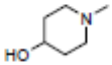
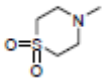
doi:10.1016/j.bmcl.2005.11.047

Azurity Pharmaceuticals, Inc. EXHIBIT - 1011

Abstract—The discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK_1) receptor antagonists is described. The evaluation of this class is briefly outlined, leading to the identification of netupitant **21** and befetupitant **29**, two new proprietary chemical entities with high affinity and excellent CNS penetration.

Table 4. Pyridines: amine substitution in the 6-position



Compound	NR^1R^2	hNK_1 K_i^a (nM)	Gerbil foot tapping[b] (ID_{50} mg/kg po)
21 (netupitant)		0.95	0.5
29 (befetupitant)		1.0	0.2
30		0.40	0.5
31		1.3	0.8

Moreover, recent clinical trials have demonstrated an important therapeutic application for NK_1 receptor antagonists in the control of cancer chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression.[4] MK-869 (aprepitant) was the first NK_1 receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.[5]

Preferred compounds were tested for their potential to pharmacologically block central NK_1 receptors in gerbils. Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK_1-selective receptor agonist GR73632.[11] Excellent oral antagonist activity was observed for the pyridine derivatives from class **E** as exemplified for netupitant (**21**), befetupitant (**29**) and structurally closely related compounds such as **30** and **31** (Table 4).[12]

In conclusion, rapid multidimensional optimization of the aryl-substituted isoxazole screening hit cluster (e.g., **1**) gave rise to 9 novel achiral structural classes (**A–I**) of highly potent and selective NK_1 receptor antagonists.[10] Pyridine derivatives from class **E** have been shown to potently inhibit NK_1 agonist-induced foot tapping behaviour in gerbils after oral administration.[12]

EX1011, 1362, 1364-65, Table 4

Grounds References: Bös (EX1014)
Netupitant as Promising NK1 Receptor Antagonist

(12) **United States Patent**
Bös et al.

(10) **Patent No.: US 6,297,375 B1**
(45) **Date of Patent: Oct. 2, 2001**

(54) **4-PHENYL-PYRIDINE DERIVATIVES**

(75) Inventors: **Michael Bös**, Montreal (CA); **Quirico Branca**, Binningen (CH); **Guido Galley**, Rheinfelden (DE); **Thierry Godel**, Basel (CH); **Torsten Hoffmann**, Birsfelden (CH); **Walter Hunkeler**, Magden (CH); **Patrick Schnider**, Oberwil (CH); **Heinz Stadler**, Rheinfelden (CH)

(73) Assignee: **Hoffmann-La Roche Inc.**, Nutley, NJ (US)

(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

(21) Appl. No.: **09/507,456**

(22) Filed: **Feb. 22, 2000**

(30) **Foreign Application Priority Data**

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Nov. 29, 1999 (EP) 99123689

(51) **Int. Cl.**[7] **C07D 213/82**; C07D 401/12; C07D 413/12; A61P 25/00; A61P 31/44

(52) **U.S. Cl.** **544/60**; 546/309; 546/194; 546/279.1; 546/316; 544/360; 544/365; 544/295; 544/131

(58) **Field of Search** 546/309, 194, 546/279.1, 316; 544/360, 365, 295, 131, 60

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Primary Examiner—Mukund J. Shah
(74) *Attorney, Agent, or Firm*—George W. Johnston; William H. Epstein; Arthur D. Dawson

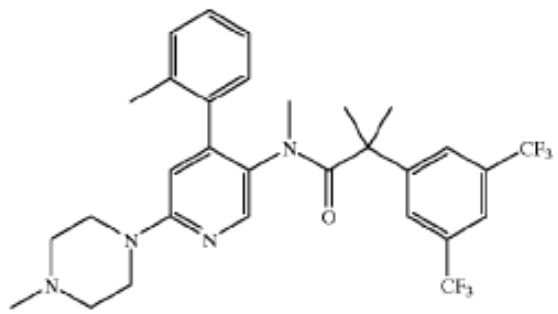
(57) **ABSTRACT**

The compounds of the related invention are related to 4-phenyl-pyridine derivatives connected by a bridge containing oxygen or nitrogen to a phenyl derivative.

65 Claims, No Drawings

Neurokinin 1 receptor antagonists are being developed for the treatment of a number of physiological disorders associated with an excess or imbalance of tachykinin, in particular substance P. Examples of conditions in which substance P has been implicated include disorders of the central nervous system such as anxiety, depression and psychosis (WO 95/16679, WO 95/18124 and WO 95/23798).

The neurokinin-1 receptor antagonists are further useful for the treatment of motion sickness and for treatment induced vomiting. The New England Journal of Medicine, Vol. 340, No. 3 190–195, 1999 has been described the reduction of cisplatin-induced emesis by a selective neurokinin-l-receptor antagonist. US 5,972,938 describes a method for treating a psychoimmunologic or a psychosomatic disorder by administration of a tachykinin receptor, such as NK-1 receptor antagonist.



and to pharmaceutically acceptable acid addition salts thereof.

The compound of formula Ib and its salts is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P) The present compound of formula Ib and its pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide was also tested as an antiemetic agent in Ferrets. Emesis was induced in Ferrets by various emetogens (apomorphine, morphine, ipecacuanha, cisplatin and $CUSO_4$. Pretreatment of this compound (0.3 mg/kg, p.o.) 2 hours before the emetigen, completely blocked the emesis induced by all emetogens. A full dose-response curve was

EX1014, 1:49-67, 14:15-39, 19:10-20

Grounds References: ALOXI (EX1015)
Effective Dosing and Administration of Palonosetron

HIGHLIGHTS OF PRESCRIBING INFORMATION
These highlights do not include all the information needed to use ALOXI Capsules safely and effectively. See full prescribing information for ALOXI.

ALOXI (palonosetron HCl) Capsules
Initial U.S. Approval: 2003

----------INDICATIONS AND USAGE----------
ALOXI Capsules, a serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist, are indicated for:
- Moderately emetogenic cancer chemotherapy -- prevention of acute nausea and vomiting associated with initial and repeat courses (1.1)

----------DOSAGE AND ADMINISTRATION----------
Adult Dosage: one 0.5 mg capsule administered approximately one hour prior to the start of chemotherapy (2.1)

ALOXI can be taken with or without food (12.3)

----------DOSAGE FORMS AND STRENGTHS----------
0.5 mg capsule (3)

----------CONTRAINDICATIONS----------
ALOXI is contraindicated in patients known to have hypersensitivity to the drug or any of its components (4)

----------WARNINGS AND PRECAUTIONS----------
- Hypersensitivity reactions may occur in patients who have exhibited hypersensitivity to other 5-HT$_3$ receptor antagonists (5.1)

----------ADVERSE REACTIONS----------
No adverse reactions have been reported at an incidence of ≥5% for the 0.5 mg dose. Headache and constipation are the most common adverse reactions but occur less frequently (6)

To report SUSPECTED ADVERSE REACTIONS, contact EISAI at 1-888-422-4743) or FDA at 1-800-FDA-1088 or *www.fda.gov/medwatch*.

----------DRUG INTERACTIONS----------
The potential for clinically significant drug interactions with palonosetron appears to be low (7)

----------USE IN SPECIFIC POPULATIONS----------
Safety and effectiveness in patients below the age of 18 years have not been established (8.4)

See 17 for PATIENT COUNSELING INFORMATION and FDA-approved patient labeling.

Revised: [08/2008]

FULL PRESCRIBING INFORMATION: CONTENTS*

1 INDICATIONS AND USAGE
1.1 Prevention of Chemotherapy-Induced Nausea and Vomiting
2 DOSAGE AND ADMINISTRATION
2.1 Recommended Dosing
3 DOSAGE FORMS AND STRENGTHS
4 CONTRAINDICATIONS
5 WARNINGS AND PRECAUTIONS
5.1 Hypersensitivity
6 ADVERSE REACTIONS
6.1 Clinical Trials Experience
7 DRUG INTERACTIONS
8 USE IN SPECIFIC POPULATIONS
8.1 Pregnancy
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8.4 Pediatric Use
8.5 Geriatric Use
8.6 Renal Impairment
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8.8 Race
8.9 Gender
10 OVERDOSAGE
11 DESCRIPTION
12 CLINICAL PHARMACOLOGY
12.1 Mechanism of Action
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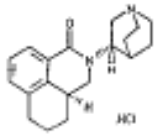
13.1 Carcinogenesis, Mutagenesis, Impairment of Fertility
14 CLINICAL STUDIES
16 HOW SUPPLIED/STORAGE AND HANDLING
17 PATIENT COUNSELING INFORMATION
17.1 Instructions for Patients
17.2 FDA-Approved Patient Labeling

* Sections or subsections omitted from the full prescribing information are not listed.

In controlled clinical trials, ALOXI Capsules have been safely administered with chemotherapeutic agents, systemic corticosteroids, analgesics, and drugs for gastrointestinal disorders including function gastrointestinal disorders, acid-related disorders, and antiemetics/antinauseants.

ALOXI (palonosetron HCl) Capsules is an antiemetic and antinauseant agent. It is a serotonin subtype 3 ($5\text{-}HT_3$) receptor antagonist with a strong binding affinity for this receptor. Chemically, palonosetron hydrochloride is: (3a<u>S</u>)-2-[(<u>S</u>)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*-benz[*de*]isoquinoline hydrochloride. The empirical formula is $C_{19}H_{24}N_2O.HCl$, with a molecular weight of 332.87. Palonosetron hydrochloride exists as a single isomer and has the following structural formula:



14 CLINICAL STUDIES

Study 1 was a multicenter, randomized, double-blind active control clinical trial of 635 patients set to receive moderately emetogenic cancer chemotherapy. A single-dose of 0.25 mg, 0.5 mg, or 0.75 mg oral ALOXI capsules given one hour prior to moderately emetogenic chemotherapy was compared to a single-dose of 0.25 mg I.V. ALOXI given 30 minutes prior to chemotherapy. Patients were randomized to either dexamethasone or placebo in addition to their assigned treatment. The majority of patients in the study were women (73%), white (69%), and naïve to previous chemotherapy (59%). The primary efficacy endpoint was Complete Response (no emetic episodes and no rescue medication) assessed in the acute phase (0-24 hours). A key secondary efficacy endpoint was Complete Response assessed in the delayed phase (24-120 hours). Other secondary endpoints included Complete Response for the acute plus delayed phases (0-120 hours) and No Nausea for the acute and delayed phases.

EX1015, 2, 3, 4

Grounds References: Herrington (EX1016) Effectiveness of Day-One Administration

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

Jon D. Herrington, PharmD, BCPS, BCOP[1]
Adam D. Jaskiewicz, PharmD[2]
Juhee Song, PhD[3]

[1] Department of Pharmacy, Scott & White Memorial Hospital, Texas A&M University Health Care System, Temple, Texas.

[2] Division of Pharmacy, The University of Texas M. D. Anderson Cancer Center, Houston, Texas.

[3] Department of Biostatistics, Scott & White Memorial Hospital, Temple, Texas.

BACKGROUND. The combination of palonosetron and aprepitant is safe and effective in the prevention of chemotherapy-induced emesis (CIE). The purpose of this pilot study was to ascertain the effectiveness of 1-day versus 3-day aprepitant in the prevention of acute and delayed nausea and vomiting in patients who were receiving highly emetogenic chemotherapy.

METHODS. This study was institutional review board-approved and informed consent was obtained before this study was begun. This was a pilot, single-institution, randomized, double-bland, placebo-controlled trial that evaluated 3 different treatment arms. All groups received palonosetron 0.25 mg intravenously on Day 1 and dexamethasone on Days 1–4. Arm A received aprepitant 125 mg orally on Day 1 followed by 80 mg on Days 2–3. Arm B received aprepitant 125 mg orally on Day 1 and placebo on Days 2–3. Arm C received placebos on Days 1–3. The primary endpoint was to evaluate the proportion of patients with acute and delayed emesis within each group.

RESULTS. Seventy-five patients were included in the analysis. The study commenced with 3 groups; however, an interim analysis displayed unacceptable emesis events in Arm C, and this group was terminated. There were no significant differences between Arms A and B for emesis, nausea, or the use of breakthrough antiemetics. In Arms A and B, 93% of patients were emesis-free from Days 1–5 compared with only 50% in Arm C.

CONCLUSIONS. From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant. *Cancer* 2008;112:2080–7. © 2008 American Cancer Society.

KEYWORDS: serotonin antagonists, antiemetic, vomiting, nausea, receptors, neurokinin-1, dexamethasone, aprepitant, palonosetron.

With the availability of palonosetron and aprepitant, the control of acute and delayed chemotherapy-induced emesis (CIE) has improved significantly. In comparison to ondansetron and dolasetron, palonosetron appears to be similar or to have enhanced efficacy in the prevention of acute and delayed CIE.[1–3]

Aprepitant is a substance P/*neu*rokinin-1 (NK1)-receptor antagonist approved for use in combination with a 5-HT_3–receptor antagonist and dexamethasone for acute and delayed CIE prevention. A 3-day oral aprepitant regimen in combination with ondansetron plus dexamethasone has displayed effectiveness against acute and delayed CIE associated with anthracycline-based breast cancer

Funded in part by MGI Pharma and Scott & White grant #R3429.

Address for reprints: Jon D. Herrington, PharmD, BCPS, BCOP, Scott & White Memorial Hospital, Department of Pharmacy, 2401 South 31st Street, Temple, TX 76508; Fax: (254) 724-4829; E-mail: jherrington@swmail.sw.org

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Azurity Pharmaceuticals, Inc. EXHIBIT - 1016

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RESULTS. Seventy-five patients were included in the analysis. The study commenced with 3 groups; however, an interim analysis displayed unacceptable emesis events in Arm C, and this group was terminated. There were no significant differences between Arms A and B for emesis, nausea, or the use of breakthrough antiemetics. In Arms A and B, 93% of patients were emesis-free from Days 1–5 compared with only 50% in Arm C.

TABLE 3
Proportion of Patients With No Emesis

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

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

EX1016, Abstract, Table 3

Grounds References: Hargreaves (EX1012)
Association of NK1 Receptor Occupancy with Efficacy

Imaging Substance P Receptors (NK_1) in the Living Human Brain Using Positron Emission Tomography

Richard Hargreaves, Ph.D.

Substance P (SP)–neurokinin-1 (NK_1) receptor pathways have been implicated in the pathophysiology of emesis and depression. Autoradiographic studies in monkey and human brains have shown a high expression of NK_1 receptors in regions important for the regulation of affective behaviors and the neurochemical response to stress. Furthermore, clinical studies demonstrated that treatment with the SP (NK_1 receptor) antagonist (SPA) aprepitant (also known as MK-0869) significantly improves depression symptoms and reduces the incidence of chemotherapy-induced nausea and vomiting. An important objective of all neuroscience drug discovery and development programs is to establish the correlation between dose, receptor occupancy, and the observed clinical effect (the dose-response relationship). These goals can be achieved using radioactive receptor-specific tracers and dynamic noninvasive brain imaging modalities, such as positron emission tomography (PET). In the SPA program, a tracer [^{18}F]SPA-RQ was chosen for PET studies on the basis of several criteria, including high affinity for the NK_1 receptor, low nonspecific binding, and good blood-brain barrier penetration. PET imaging studies in rhesus monkeys and humans confirmed these tracer features and established the usefulness of this probe for in vivo NK_1 receptor occupancy studies. Subsequent PET occupancy studies in humans predicted that very high levels of central NK_1 receptor occupancy (> 90%) were associated with therapeutically significant antidepressant and antiemetic effects. Future PET imaging studies will focus on quantification of NK_1 receptor expression in depressed patients, both before and after successful treatment with antidepressants. *(J Clin Psychiatry 2002;63[suppl 11]:18–24)*

Substance P (SP) is an 11-amino-acid residue molecule that belongs to the group of peptides known as neurokinins (NKs). SP exerts its biological effects by binding to and activating the NK_1 receptor. The SP-NK_1 receptor pathway is the most abundant and the most extensively studied NK pathway in both the central nervous system (CNS) and the peripheral nervous system (PNS),[1] where it plays an important role in the regulation of response to a broad range of inflammatory, noxious, and stressful stimuli. In the spinal cord, SP is thought to be involved in nociception and sensitization "wind-up" phenomena, but clinical studies of SP (NK_1 receptor) antagonists (SPAs) in somatic pain have to date been negative.[2] High concentrations of SP are also present in the brain stem nuclei, nucleus tractus solitarius, and area postrema, regions that have been implicated in the control of the vomiting reflex.[3] A role for SP in the regulation of emesis is further supported by observations that local application of SP to the area postrema causes retching in ferrets and that the chemotherapeutic agent cisplatin increases plasma levels of SP in cancer patients.[4] Most importantly, SPAs were recently shown to block emesis in animal models and to prevent acute and delayed chemotherapy-induced nausea and vomiting (CINV) in the clinic.[5,6]

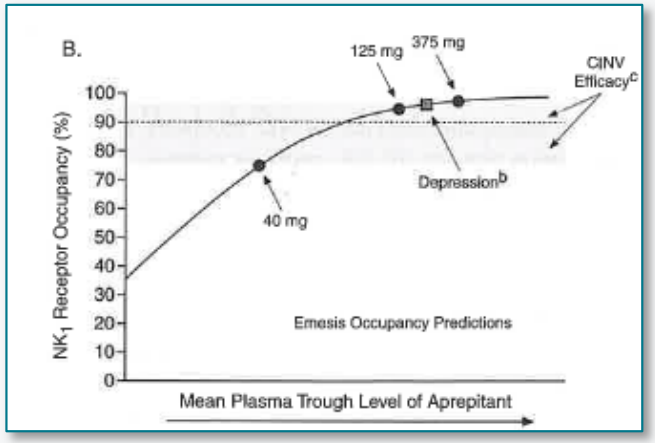
Receptor mapping studies have shown that the SP-NK_1 receptor system is also expressed in brain regions involved in the regulation of affective behaviors and the neurochemical response to stress.[7–9] Despite some interspecies differences in the expression of NK receptors,[10] NK_1 receptors predominate in the brain of gyrencephalic species. Specific autoradiographic [^{125}I]SP binding studies in human and monkey brains demonstrate the greatest abundance of NK_1 receptors in the amygdala, nucleus accumbens, septum, caudate, and putamen, with moderately high levels in the hippocampus, hypothalamus, locus ceruleus, substantia nigra, and the frontal and olfactory cortices. This observation, together with the significant neuroanatomical spatial overlap of the SP-NK_1 receptor system with that of monoamine neurotransmitter pathways (serotonin [5-hydroxytryptamine [5-HT]] and norepinephrine), suggested that the SP-NK_1 receptor pathway may be involved in the modulation of affective behaviors.

Collective evidence from preclinical and clinical studies with highly selective nonpeptide SPAs further supported this idea. In gerbils, the anxiety-like stress behavior of foot tapping could be induced by central infusion of the NK_1 receptor agonist GR73632 and strongly inhibited by

From Merck Research Laboratories, West Point, Pa.
Supported by an unrestricted educational grant from Merck & Co., Inc.
This article reviews the work of many people in Merck Research Laboratories in Terlings Park, U.K.; West Point, Pa.; and Blue Bell, Pa., and excellent collaborations with academic PET centers in Uppsala, Sweden; Turku, Finland; and Hammersmith, U.K. Merck Imaging Research is very grateful to all for their input in the [^{18}F]SPA-RQ program.
Corresponding author and reprints: Richard Hargreaves, Ph.D., Merck Research Laboratories, West Point, PA 19486 (e-mail: Richard_Hargreaves@merck.com).

Substance P (SP)–neurokinin-1 (NK_1) receptor pathways have been implicated in the pathophysiology of emesis and depression. Autoradiographic studies in monkey and human brains have shown a high expression of NK_1 receptors in regions important for the regulation of affective behaviors and the neurochemical response to stress. Furthermore, clinical studies demonstrated that treatment with the SP (NK_1 receptor) antagonist (SPA) aprepitant (also known as MK-0869) significantly improves depression symptoms and reduces the incidence of chemotherapy-induced nausea and vomiting. An important objective of all neuroscience drug discovery and development programs is to establish the correlation between dose, receptor occupancy, and the observed clinical effect (the dose-response relationship). These goals can be achieved using radioactive receptor-specific tracers and dynamic noninvasive brain imaging modalities, such as positron emission tomography (PET). In the SPA program, a tracer [^{18}F]SPA-RQ was chosen for PET studies on the basis of several criteria, including high affinity for the NK_1 receptor, low nonspecific binding, and good blood-brain barrier penetration. PET imaging studies in rhesus monkeys and humans confirmed these tracer features and established the usefulness of this probe for in vivo NK_1 receptor occupancy studies. Subsequent PET occupancy studies in humans predicted that very high levels of central NK_1 receptor occupancy (> 90%) were associated with therapeutically significant antidepressant and antiemetic effects. Future PET imaging studies will focus on quantification of NK_1 receptor expression in depressed patients, both before and after successful treatment with antidepressants. *(J Clin Psychiatry 2002;63[suppl 11]:18–24)*

tors requires aprepitant doses ≥ 100 mg. Curve fitting to the plasma concentration–receptor occupancy curves showed that high levels of NK_1 receptor occupancy were associated with significant antidepressant effects and optimal activity against CINV. Both the 300-mg dose of aprepitant used in the treatment of depression and the initial 125-mg dose studied for treatment of emesis blocked ≥ 90% of NK_1 receptors in the CNS (Figure 6B), whereas the initial 40-mg dose used in the study of emesis resulted in lower (75%) receptor occupancy (Figure 6B). Interestingly, this analysis also illustrates why a 375-mg dose of aprepitant had no advantage over the 125-mg dose in the treatment of CINV,[19] since the NK_1 receptor occupancies achieved by these doses were essentially the same.



EX1012, Abstract, 23, Fig. 6B

Grounds References: Bonadeo (EX1017)
Palonosetron Purity

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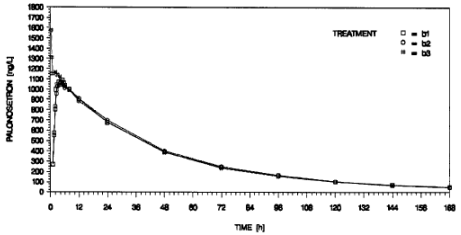
Published:
— *with international search report*

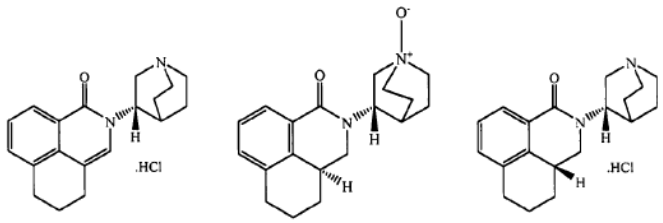
(54) Title: SOFT CAPSULES COMPRISING PALONOSETRON HYDROCHLORIDE HAVING IMPROVED STABILITY AND BIOAVAILABILITY



(57) Abstract: Provided are solid oral dosage forms of palonosetron hydrochloride, methods of using the dosage forms to treat emesis, and methods of making the dosage forms. The dosage forms have improved stability and bioavailability, and are preferably in the form of liquid filled capsules.

WO 2008/049552 A1

The palonosetron hydrochloride used to make the dosage form, or contained in the final dosage form, may also be characterized by the presence of various palonosetron related compounds, including compounds Cpd3, Cpd2, and/or Cpd1, as described by the following chemical structures:



2- [(3S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,4,5,6-tetrahydro-1*H*-benzo[*de*] isoquinoline -1-one hydrochloride	(3S)-3-[(3aS)-1-oxo-2,3,3a,4,5,6-hexahydro-1*H*-benzo[*de*] isoquinoline-2-yl]-1-azoniabicyclo[2.2.2]octan-1-olate	(3aR)-2-[(S)-1-Azabicyclo [2.2.2]oct-3-yl]-2,3,3a,4,5,6-hexahydro-1-oxo-1*H*benz[*de*] isoquinoline hydrochloride
Cpd2	Cpd1	Cpd3

measured in the dosage form since it is a measure of oxygen mediated degradation. In one preferred embodiment, the dosage forms are defined by a stability in which no more than about 5.0 wt.%, 4.0 wt.%, 3.0 wt.%, 2.5 wt.%, 2.0 wt.%, 1.5 wt.%, 1.0 wt.%, or 0.5 wt.% of compound Cpd1, are formed when the dosage form in its moisture resistant packaging is exposed to an environment of 25 °C and 60% RH, or 40 °C and 75% RH, for periods equal to or exceeding 3 months, 6 months, 9 months or even one year.

incorporated by reference herein in their entirety. The resulting soft gelatin capsule is soluble in water and in gatrointestinal fluids. Upon swallowing the capsule, the gelatin shell rapidly dissolves or ruptures in the gastrointestinal tract thereby introducing the pharmaceutical actives from the liquid core into the body.

EX1017, 11-12, 16

Claims Recite Using Known Options in Standard Protocol

- Claims use same standard of care, specifying known 5-HT3 and NK1 antagonists:

e.g., '826 claim 1:

Netupitant taught by Bös or Hoffmann:

- NK1 antagonist

Both components already incorporated in protocol (MASCC & Herrstedt):

- 5-HT3 antagonist
- dexamethasone

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

a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK_1) receptors in the striatum seventy-two hours after said administration;

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

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

wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

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

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

EX1001, claim 1; EX1010; EX1011; EX1013; EX1014

Claims' Use of Known Class Members Was Obvious

- Claims' use of known 5-HT3 and NK1 antagonists in a standard protocol is unpatentable
- Similar to obviousness of *KSR*'s using "known technique…to improve similar devices." 550 U.S. 398 (2007); *see also id.* ("mere substitution of one element for another known in the field" obvious if not shown to "do more than yield a predictable result")
- Institution decisions correctly recognized obviousness of claims

On the current record, we are unpersuaded by Patent Owner's arguments because Patent Owner fails to rebut Petitioner's reason for substituting netupitant for aprepitant. Patent Owner does not dispute that aprepitant and netupitant were both known NK_1 receptor antagonists, and it is obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) ("[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another.").

MEC or HEC. Pet. 17; Ex. 1013, 22. MASCC also specifically suggests palonosetron as the preferred choice of 5-HT_3 antagonist, as recited in claim 19. Pet. 20 (citing Ex. 1013, 24 ("Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists.")). Finally, as for choice of NK_1 antagonist, Hoffmann identifies netupitant as a promising candidate. Ex. 1011, Abst.

945-ID, 26, 29; *see also* 946-ID, 18-22; 947-ID, 21-24; 948-ID, 15-19; 949-ID, 14-18

None of PO's Arguments Undermine Obviousness

- No claim requirement of statistically significant treatment of nausea
  - Not supported by claim language
  - Prior art taught treatment of both nausea and vomiting
  - Dexamethasone itself treats nausea
- Motivation to combine established
  - Hoffmann/Bös single out netupitant for praise
  - Existence of alternatives irrelevant (*see Mouttet/Par Pharm)*
- Expectation of success does not require a certainty of superior clinical outcome
- Purported unexpected results:
  - No nexus
  - No comparison to closest prior art

945-DI, 26, 29

WILSON
SONSINI

Claim Construction

POR's New Construction Not Supported

945-POR, 18, 20:

> For all of these reasons, each of claims 1 and 19 should be construed to require that the claimed regimen treats ***both*** nausea ***and*** vomiting to a statistically significant degree ($p<0.05$), as compared to baseline.

> Claims 1 and 19 would both be understood by a POSA as claiming a method of treatment that shows improved efficacy to a ***statistically significant degree*** relative to a defined baseline. This construction reflects a POSA's natural reading

- As explained in Replies, this new construction is unsustainable:
  - Independent claims do not define a baseline for comparison, so importing one would render them indefinite
  - Even if statistical significance were imported, the baseline must broadly include any comparator, including no treatment or ineffective treatment

945-POR, 16-20; 945-Reply, 2-6

POR's New Construction Not Supported

- '826 Claim 1 confirms that PO's proposed baseline is incorrect:
  - Claim expressly discusses comparison to ineffective treatment (palonosetron and sub-therapeutic dose of dexamethasone alone)
  - This comparison reflects property of NK1 antagonists to double dexamethasone AUC, as known in the prior art (EX1010, 147 "two-time increase in the AUC of dexamethasone" when co-administered with NK1 antagonist)
  - No claim language supporting baseline of palonosetron + therapeutic level of dexamethasone

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

a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK_1) receptors in the striatum seventy-two hours after said administration;

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

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

wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

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

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

945-POR, 16-20; 945-Reply, 2-6

POR's New Construction Not Supported

- Independent claims 1-2 and 4 of '357 patent and 1-2 of '297 patent further confirm PO's construction is wrong, as they lack any comparator at all:

EX1002, claims 1-2, 4:

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.

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.

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.

EX1004, claims 1-2:

1. A method of preventing acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

2. A method of achieving complete response during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising inducing in said subject therapeutically effective blood levels of palonosetron and netupitant in a combination regimen with dexamethasone.

946-Reply, 4-5; 947-Reply, 4-5; 949-Reply, 3-5

POR's New Construction Not Supported

- No support in specification for PO's assertion that claims require "standard therapy" as a baseline (945-POR, 7, 20)
- Specification only uses the term "baseline" once, referring generically to any baseline; it never equates it to the "standard therapy" asserted in the POR:

> As used herein, the term "significantly" refers to a level of statistical significance. The level of statistical significant can be, for example, of at least $p<0.05$, of at least $p<0.01$, of at least $p<0.005$, or of at least $p<0.001$. Unless otherwise specified, the level of statistical significance is $p<0.05$. When a measurable result or effect is expressed or identified herein, it will be understood that the result or effect is evaluated based upon its statistical significance relative to a baseline. In like manner, when a treatment is described herein, it will be understood that the treatment shows efficacy to a degree of statistical significance.

- Effectiveness in treating both nausea and vomiting was well-recognized in prior art

945-POR, 7, 20; EX1001, 8:24-34; 945-Reply, 5

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Level of Ordinary Skill

Level of Ordinary Skill in the Art

- POSA skilled in clinical medicine, medical oncology, radiation oncology, oncology nursing, pharmacy, or pharmacology (945-Pet., 8, as modified at 945-ID, 11)
- Dr. Peroutka describes POSAs' educational background and working team (EX1009, ¶59):
- Institution decision correctly rejected requirement of being an oncologist.
- As Dr. Roeland conceded, outcome is the same under either definition (EX2088 ¶28).

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

- Consistent with findings at institution. See 945-ID, 11-12 (noting "our analysis would be the same under either party's definition of a POSA," and finding Dr. Peroutka "qualified to testify from the perspective of a POSA" and had oncology training)
- Regardless, grounds show obviousness based on teachings of references, not expert gap-filling

945-Pet., 8; EX1009, ¶59; EX2088, ¶28; 945-ID, 11-12; 945-Reply, 9-11

PO's Arguments Lack Adequate Expert Support

- Patent Owner abandoned reliance on Dr. Navari post-institution, turning to Dr. Roeland instead
- Roeland's opinions are undermined by his low qualifications and lack of diligence preparing his declarations
- Roeland declaration contained no structural or pharmacokinetic comparison between aprepitant and netupitant
- Roeland declaration advances conclusory opinions without foundation in legal standards. *See* EX1067, 101:19–103:2 (admitting no legal background and no foundation in legal standard)

945-Reply, 11-12

PO's Arguments Lack Adequate Expert Support

Q Okay. Is it correct that you are not a biochemist?
A That is correct.
Q Is it correct that you are not a pharmacologist?
A That is correct.
Q Is it correct that you are not an attorney?
A That is true.
Q Is it correct that you do not have a PhD?
A That is true.
Q Is it correct that you are not a pharmaceutical scientist?
A I am not a pharmaceutical scientist.
Q Is it correct that you are not a statistician?
A I am not a statistician.

Q And when were you certified by them as a medical oncologist?
A In January of 2013.

Is there anything you can point me to in your declaration that provides legal standards that you rely on for your opinions in this case?
A So I think, as you're quite aware, I'm not a lawyer. So I'm not sure what you're getting at.
Q Well -- yeah. So there's no disclosure in your declaration of any legal standards that you are applying; is that correct?
A I'm struggling to understand what you're trying to say here.

Q Right. So I understand you're not a lawyer. But you're telling us that you don't have any understanding as to what the legal standards are for objective indicia; is that correct?
A If you were to ask me all the points required for objective indicia with regard to legal terms, I cannot answer that.

945-Reply, 10-12; EX1067, 80:25-81:14, 104:13-22, 108:15-21

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IPR2025-00945 Grounds 1-3: MASCC + Hoffmann / Bös / ALOXI

Motivation to Combine: MASCC & Hoffmann

- Closest prior art: MASCC
  - Same 3-drug architecture (NK1 antagonist + 5-HT3 antagonist + dexamethasone)
  - Palonosetron is preferred 5-HT3 antagonist
  - Describes aprepitant as merely "the first" of a *new class* of NK1 antagonists, inviting successors
- Hoffmann specifically identifies netupitant and one other drug as alternatives in aprepitant's class of NK1 antagonists, touting netupitant's:
  - high affinity
  - excellent CNS penetration
  - excellent oral NK1-antagonist activity

Aprepitant is the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT3-receptor antagonist plus dexamethasone [4].

Palonosetron is a 5-HT3-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT3 receptor antagonists. Two studies in patients treated with

Preferred compounds were tested for their potential to pharmacologically block central NK_1 receptors in gerbils. Animals were orally pretreated (2 h) with the test compound followed by central injection (icv) of the NK_1-selective receptor agonist GR73632.[11] Excellent oral antagonist activity was observed for the pyridine derivatives from class **E** as exemplified for netupitant (**21**), befetupitant (**29**) and structurally closely related compounds such as **30** and **31** (Table 4).[12]

Abstract—The discovery of a novel, achiral pyridine class of potent and orally active neurokinin-1 (NK_1) receptor antagonists is described. The evaluation of this class is briefly outlined, leading to the identification of netupitant **21** and befetupitant **29**, two new proprietary chemical entities with high affinity and excellent CNS penetration.

945-Reply, 19, 22-23

Motivation to Combine: MASCC & Bös

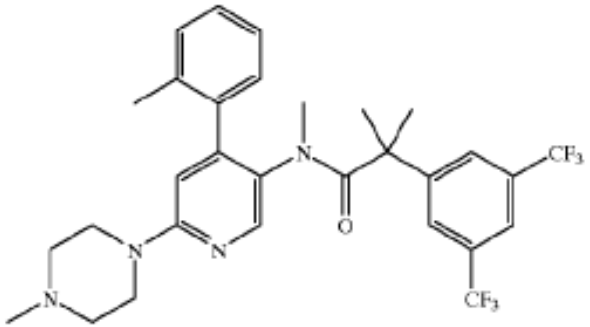
- Bös also singled out netupitant as one of only three compounds selected for testing as an alternative to aprepitant
- Bös choice of netupitant as one of a handful of compounds actually characterized with data, in combination with desirable properties, provides ample reason for POSA to select as NK1 antagonist

The affinity of the compound of formula Ib for the NK_1 receptor was evaluated at human NK_1 receptors in CHO cells infected with the human NK_1 receptor (using the Semliki virus expression system) and radiolabelled with [^{3}H] substance P (final concentration 0.6 nM). Binding assays were performed in HEPES buffer (50 mM, pH 7.4) containing BSA (0.04%) leupeptin (8 μg/ml), $MnCl_2$ (3mM) and phosphoramidon (2 μM). Binding assays consisted of

The compound of formula Ib is a potent and selective antagonist at recombinant human neurokinin, (NK_1) receptors expressed in CHO cells. It has an affinity (pKi) of 9.0 for the human NK_1 receptor and over 2 orders of magnitude of selectivity for the NK_1 receptor compared to NK_2 and NK_3 receptors and compared to over 50 other binding sites that have been evaluated.

Another embodiment of this invention is a compound of formula I (2-(3,5-bis-trifluoromethyl-phenyl)-N-methyl-N-[6-(4-methyl-piperazin-1-yl)-4-o-tolyl-pyridin-3-yl]-isobutyramide) which has the formula Ib

Ib



and to pharmaceutically acceptable acid addition salts thereof.

The compound of formula Ib and its salts is also characterized by valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P) The present compound of formula Ib and its pharmaceutically acceptable salts can be prepared by methods known in the art, for example, by processes described below, which process comprises

EX1014, 14:9-38, 17:60-18:48

Motivation to Combine: Netupitant from Hoffmann/Bös

- Potential existence of alternative solutions does not defeat obviousness, regardless of different alternatives were superior or inferior. *See In re Mouttet*; *Par Pharm.*
- Netupitant was identified as one of a narrow set of promising leads, with Hoffmann/Bös narrowing the field to a handful with data
- As institution decisions correctly recognized, this suffices to show obviousness:

948-ID, 18-19; 949-ID, 19; *see* 945-ID, 25:

> We are not persuaded by these arguments. The fact that multiple solutions to the problem of treating CINV may have been obvious is not probative that the combination proposed by Petitioner is non-obvious. The law expressly contemplates that there can be more than one obvious solution to the same problem. Indeed, an inferior solution can still be obvious even when a superior solution is also available. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) ("[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes."); *Bayer Pharma AG v. Watson Lab'ys, Inc.*, 874 F.3d 1316, 1327 (Fed. Cir. 2017) ("When there are only two possible formulations and both are known in the art at the time, the fact that there may be reasons a skilled artisan would prefer one over the other does not amount to a teaching away from the lesser preferred but still workable option."). Further, obviousness "does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away." *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014).

946-ID, 29; 947-ID, 28-29:

> We have considered, but are not persuaded by, Patent Owner's arguments to the contrary at this stage. We find unavailing Patent Owner's contention that a POSA would not have had a sufficient reason to select netupitant among millions of other compounds disclosed in Bös. Compound Ib is extensively highlighted in Bös among other NK_1 antagonists, and was the subject of both *in vitro* testing and animal studies showing potential utility in the treatment of emesis. Ex. 1010, 14:9–19:30. To be sure, Bös does not include any comparative analysis between netupitant and aprepitant, nor does it include data assessing netupitant's potential efficacy in controlling nausea. Such data, however, is not necessary to provide the requisite reason to combine. Although the inventors purport to have

Reply, 19

Reasonable Expectation of Success

- Required expectation is success in making the claimed combination, not in achieving any particular clinical endpoint.
- Netupitant and aprepitant were both known NK1 antagonists acting through the same mechanism to CINV when administered prior to chemotherapy
  - Using one known, structurally-related compound for another to achieve the same purpose the same way is textbook obviousness. *See, e.g., KSR, In re Omeprazole*
- Showing of reasonable expectation of success correctly recognized at institution:

success."). Thus, Petitioner must show that a POSA would have had a reasonable expectation of success in modifying MASCC's combination therapy for treating CINV by substituting netupitant for aprepitant. Framed properly, the record evidence shows adequate support for a reasonable expectation of success. The POSA would need to only substitute one known NK_1 antagonist for another. *See* Ex. 1011, Abst. (Hoffmann teaching netupitant as a potent and orally active NK_1 receptor antagonist having "excellent CNS penetration."); *see also* Ex. 1009 ¶ 136 ("[A] POSA would have had an extremely high likelihood of succeeding in substituting netupitant for aprepitant for antiemetic combination therapy because both compounds are NK_1 receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK_1 receptor antagonism) when administered prior to chemotherapy.").

On the current record, we are unpersuaded by Patent Owner's arguments because Patent Owner fails to rebut Petitioner's reason for substituting netupitant for aprepitant. Patent Owner does not dispute that aprepitant and netupitant were both known NK_1 receptor antagonists, and it is obvious to those skilled in the art to substitute one known equivalent for another. *See In re Omeprazole Patent Litigation*, 483 F.3d 1364, 1374 (Fed. Cir. 2007) ("[T]his court finds no . . . error in [the] conclusion that it would have been obvious to one skilled in the art to substitute one ARC [alkaline reactive compound] for another.").

945-Pet., 22-23, 27-28; 945-ID, 20, 26

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IPR2025-00945 Grounds 4-7: Herrstedt + Hoffmann / Bös + Hargreaves/Herrington/ALOXI

Claim 1

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

a) administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK_1) receptors in the striatum seventy-two hours after said administration;

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

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

wherein said first dose of dexamethasone comprises from 50 to 70% of a minimum effective dose when administered alone against CINV;

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

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

- Claim 1's comparator is expressly an ineffective combination
- Any triple-therapy combination that restores dexamethasone's known effectiveness satisfies claim limitations
  - NK1 antagonists known to double dexamethasone's effective AUC
  - See 945-Pet., 38-43; 945-Reply, 3-4, 15-17
  - Herrstedt provides triple-therapy standard of care
  - Hoffmann/Bös single out netupitant as NK1 inhibitor

945-Pet., 38-43; 945-Reply, 3-4, 15-17

Dexamethasone-restoration Rebuts PO's New Claim Construction Arguments

- Petition already explained known mechanism for restoration of dexamethasone's anti-nausea properties when using NK1 antagonists with lower-dose dexamethasone
- Claim 1's language ("a therapeutically effective amount which…") confirms these properties are inherent properties, rather than further restrictions on what constitutes a therapeutically-effective amount

plus ondansetron. Dexamethasone 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%; $P < 0.02$). The combination of dexamethasone and

Dexamethasone and methylprednisolone are sensitive substrates of CYP3A4. The combination of aprepitant and oral dexamethasone results in a two-time increase in the AUC of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism. When methylprednisolone is given in combination with aprepitant the intravenous dose can be reduced by 25% and the oral dose by 50% to obtain the same exposure of methylprednisolone, when given without concomitant administration of aprepitant [44]. Dexamethasone is an inducer of CYP3A4, but concomitant administration of dexamethasone and ondansetron has no clinically relevant impact on the AUC of aprepitant.

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

945-Pet., 9-10, 38-43; 945-Reply, 3-4, 15-17; EX1009, ¶115; EX1010, 147; EX1013, 24

Dexamethasone-restoration Rebuts PO's New Claim Construction Arguments

- POR advanced new theory of patentability, importing a requirement of statistically-significant treatment of nausea into the claims
- '954 claim 1 confirms this construction is wrong
- Dexamethasone's established effect in treating nausea alone confirms prior art treated nausea better than no treatment

placebo/full dexamethasone. Hence, claim 1 fudges the comparator by comparing an ***explicitly ineffective*** amount of dexamethasone with the same amount of dexamethasone that has NK_1-inhibitor-***doubled*** effectiveness: of course, the comparator will be ineffective by definition; however, using an NK_1-inhibitor restores its effectiveness. Thus, properly understood, claim 1's "improvement" requirement is met simply by restoring dexamethasone's effectiveness against nausea from an ineffective half-dose back to a full-dose via NK_1-inhibitor enhancement. Netupitant, an NK_1-inhibitor, would be expected to do this.

945-Pet., 9-10, 38-43; 945-Reply, 3-4, 15-17

Herrstedt's Complete Response/Complete Protection Satisfies Claim 1

- Claim 1 recites treatment of "both nausea and vomiting to a greater extent" than without netupitant
  - This is satisfied by net improvement on combined endpoint
  - No requirement of separate improvement for nausea in isolation

asone days 2–4 plus aprepitant days 2–3. In the Hesketh study [37], a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen ($P < 0.001$), and in the Poli-Bigelli study [38] complete response rates were 62.7% versus 43.3% ($P < 0.001$). The most recently published HEC study [39] used the same design, except that ondansetron was included in the control arm for delayed protection days 2–4. Again a statistically benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm ($P = 0.003$). In the first two studies, a difference of approxi-

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.

945-Pet., 50; 945-Reply, 3-4; EX1010, 146; EX1039, Table 2; EX1030, Table 1

Proposed Combination Satisfies Claim 1's Striatum-Occupancy Limitation

- Claim 1: "…which enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK1) receptors in the striatum seventy-two hours after said administration"
  - Descriptive/inherent consequence of administering ***any*** therapeutically effective netupitant dose
  - Confirmed by claim language ("which…"); *see* 945-Reply, 7-8 (citing *Minton v. NASD*)
  - No requirement of separate prior art disclosure
  - Inherency consistent with prosecution findings. *See* EX1008, 120.

945-Pet., 34-37; 945-Reply, 7-8; EX1008, 120

Proposed Combination Satisfies Claim 1's Striatum-Occupancy Limitation

- Hargreaves shows prior art's own methodology: striatum NK1-receptor occupancy above ~75% is recognized proxy for antiemetic therapeutic effectiveness in general, not limited to netupitant
  - Syllogism:
    - Any therapeutically effective dose of any NK1 antagonist reaching the CNS occupies receptors at this level
    - Netupitant is an NK1 antagonist that reaches the CNS
    - Any therapeutically effective dose of netupitant occupies receptors at this level, and thus satisfies the recited claim limitation

945-Reply, 19-20; EX1012, 23, Fig. 6B

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IPR2025-00946 through -00949: combinations involving Herrstedt and Bös

Grounds IPR2025-00946 through -00949 Parallel IPR2025-00945

- Each ground in IPR2025-00946 through -00949 relies on Herrstedt+Bös, on their own or in combination with other references
- Challenged claims obvious for reasons generally parallel those in IPR2025-00945
- Additional ground- and claim-specific arguments addressed below

IPR2025-00948, Claim 11

- Claim 11 directed to single-dose for five days:
- Herrington's one-day dosing of aprepitant sufficient for multi-day coverage, motivating single-day dosage, with benefits including increased simplicity and patient compliance
- Bös's disclosure of 30-hour half life corroborates expectation of effectiveness for five-day coverage based on Herrington
- No burden to run same comparative PK study as in patent; only reasonable expectation of success is required

11. A method of treating nausea and vomiting in response to an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising administering to said patient netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which is effective to treat nausea and vomiting during the acute and delayed phases of emesis, wherein said therapeutically effective amount of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if effective to treat said nausea and vomiting for said five consecutive days.

948-Pet, 20-21; EX1003, claim 11

IPR2025-00949, Claim 23

23. The method of claim **3**, wherein said blood levels of netupitant are independently effective to prevent nausea in a subject receiving highly emetogenic cancer chemotherapy.

- No dispute that claim 23's "independently effective" language refers to effect added by inclusion of netupitant in multidrug combination (*see* 949-Pet., 33)
- Addition of netupitant to palonosetron and dexamethasone is mechanistically linked to nausea prevention, as it unlocks dexamethasone's restored effectiveness, consistent with known behavior of NK1 antagonists
- PO's own data confirm this property of netupitant (EX1009, ¶816 (citing EX1004, 16:1-40 (Example 3)):

palonosetron hydrochloride. Similarly with regard to netupitant, the netupitant-dexamethasone drug interaction study (EX1004 ('297 patent), 16:1-40) shows iterative increase of dexamethasone bioavailability with each of 100 mg, 300 mg, and 450 mg doses. The 300 mg dose did not provide any particular benefits. *Id.*;

949-Pet., 33, 41-42; EX1009, ¶816; EX1004, 16:1-40, claim 23

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No Secondary Indicia Shown

"Synergy" Is Property of Palonosetron, Not Netupitant

- Data from prosecution showed equivalent overall anti-nausea effects from palonosetron plus any NK1 antagonists, whether netupitant or aprepitant

EX1009, ¶1385 (citing EX1005, 346):

EX1005 (file history of '462 application), 346 (Declaration Table 2). As can be seen from this table, palonosetron in combination with either aprepitant or netupitant showed equivalent results for percentage of patients with no significant nausea overall (89.6% (netupitant), 88.5% (aprepitant), 91% (aprepitant)). Similarly, palonosetron in combination with either NK_1 receptor antagonist showed equivalent results for percentage of patients with no nausea overall (61.5% (netupitant), 59.9% (aprepitant)). Any other differences between the studies were in my opinion marginal and insufficient to show unexpected or surprising results.

TABLE 2

Efficacy Endpoint	1 Palo + Netu (HEC)[a]	2 Ondan + Aprep (HEC)[a]	3 Palo + Netu (MEC)[b]	4 Ondan + Aprep (MEC)[c]	4a Ondan + Aprep (HEC)[c1]	5 Palo + Aprep (HEC)[d]	6 Palo + Aprep (MEC)[e]	7 Ondan + Aprep (MEC)[f]	8 Palo + Aprep (HEC)[g]
Percentage of Patients with No Nausea									
Overall (0-120h)	61.5	58.2	50.3	33	48,49	nr	32[ncs]	30.6	59.9[ncs]
Acute (0-24h)	80.0	77.6	70.4	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	68.1*	60.4	53.3	nr	51,53	nr	nr	nr	nr
Percentage of Patients with No Significant Nausea									
Overall (0-120h)	89.6*	85.8	74.6*	61	73,71	88.5	56[ncs]	66.1	91[ncs]
Acute (0-24h)	98.5*	94.0	87.3	nr	nr,nr	nr	nr	nr	nr
Delayed (25-120h)	90.4*	88.1	76.9	nr	75,73	nr	nr	nr	nr

*Statistically Significant ($p < 0.05$)
[nr] Data Not Reported
[ncs] Non-Comparative Study; statistical significance not evaluated

945-Reply, 19-20; EX1005, 346

"Synergy" Is Property of Palonosetron, Not Netupitant

- Post-filing data confirms palonosetron's interaction with NK1 antagonists is generic

EX1045, 2637-38:

nist substance P (Stathis et al. 2012). The results suggest that palonosetron's effect is distinct in the presence of an NK_1 receptor antagonist at least in NG108-15 cells. In the present study, we began to explore the potential mechanism behind the synergistic effect. We report that when used alone, both netupitant and palonosetron can trigger NK_1 receptor internalization and that when used in combination their effect becomes additive. NK_1 receptor internalization could be a result of the previously observed $5\text{-}HT_3/NK_1$ receptor crosstalk inhibition by palonosetron (Rojas et al. 2010a).

945-Reply, 19-20; EX1012, 23, Fig. 6B

EC50: No Comparison to Closest Prior Art

- Data in table 1 of prosecution declaration (EX1005, 343 (EC50 shifts) lacked nexus to nausea and lacked any comparison between claimed combinations and closest prior art (aprepitant + palonosetron; *see, e.g.*, Herrstedt)

- Board correctly identified this deficiency at institution:

- No remedy during trial

> Having considered the parties' positions and Patent Owner's evidence of alleged unexpected results, summarized above, we are not persuaded that the evidence establishes a sufficient basis to negate Petitioner's reasonable likelihood of prevailing based on the present record. For example, with regard to the alleged synergistic effect of the netupitant + palonosetron combination on substance P inhibition shown in Table 1 of the Rule 132 Declaration, there is no comparison made to the combination of aprepitant + palonosetron taught in Herrstedt. As such, that data does not demonstrate any unexpected results compared to the closest prior art teaching. *See*

945-ID, 34; EX1005, 343; 945-Reply, 22-23; 945-Pet., 68

Herrington Does Not Support Patentability

- Herrington study does not establish that no NK1 antagonist improves nausea, only that its study failed to detect differences for aprepitant in one category

- PO fails to meet its burden of production to show improvement from netupitant, rather than palonosetron's independently-known indirect NK1 activity or to noise from underpowered studies

- Indeed, PO's own data fail to clear statistical significance in the first place at the overall/acute phase

945-Pet., 25, 50-51

Specification's Own Nausea Data Equivocal

- Large percentages in both groups being successfully treated for nausea
  - Unambiguous nausea endpoints (no nausea, total control) never reached significance at any dosage
  - Nausea-related significance only met for "no significant nausea" and "complete protection," which bundles emesis and rescue-medication control with nausea
- Any difference would constitute difference in degree at best

TABLE 6

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

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

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

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

Reply, 17-23; Pet., 62; EX1009, ¶1343; EX1001, Table 6

Independent Motivation Defeats Purported Unexpected-Results

- Hoffmann and Bös supply *independent* reasons to use netupitant: CNS penetration and oral availability

EX1009, ¶¶175, 177:

replacement for aprepitant. Moreover, a POSA would have understood that CNS penetration described by Bös was highly desirable in NK_1 receptor antagonists, as this would allow the therapeutic to cross through to the NK_1 receptors present in the central nervous system and to interfere with Substance P increases following emetogenic therapy. Indeed, the prior art explained the importance of entering the CNS for antagonism of Substance P receptors in the brain:

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

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

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

- Unexpected results insufficient where prior art provided independent reason for combination. *Allergan, Inc. v. Sandoz Inc.*, 726 F.3d 1286, 1293 (Fed. Cir. 2013)

945-Pet., 25, 50-51

No Showing of Skepticism

- PO's skepticism argument rests on Dr. Roeland's characterization of generic 2009-era doubt about NK1 antagonists and nausea

- Attributing to NK1 antagonists a "more pronounced effect" against vomiting and "less impact" on nausea (EX2088, ¶262, quoting EX1034, 2829; EX2073, 1005) confirms recognition of effect on nausea.

- "[G]eneric industry skepticism cannot, standing alone, preclude a finding of motivation to combine." *Auris Health v. Intuitive Surgical*, 32 F.4th 1154, 1159 (Fed. Cir. 2022).

945-Reply, 24-25; 945-Sur-Reply, 21-22