

Patent Owner's Demonstratives

United States Patent and Trademark Office
Before the Patent Trial and Appeal Board

Azurity Pharmaceuticals, Inc., Petitioner *v.* *Helsinn Healthcare S.A.*, Patent Owner

U.S. Patent Nos. 8,623,826, 9,186,357, 9,943,515, and 10,828,297

Cases: IPR2025-00945, -00946, -00947, -00948, and -00949 Oral

Hearing: September 15, 2026

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Agenda

- Serial motivation failures defeat every ground
- Failure to show a reasonable expectation of success
- Objective indicia confirm nonobviousness
- Failure to show that the prior art discloses every claim limitation

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U.S. Patent No. 8,623,826 (“the ‘826 Patent”)

The invention claimed is:

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 (NK₁) 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.

Ex. 1001, 21:39-63

19. A method of treating both nausea and vomiting in a human subject in need thereof during the acute or delayed phases of chemotherapy induced nausea and vomiting (CINV) in response to moderately or highly emetogenic chemotherapy, comprising administering to said subject before said chemotherapy a therapeutically effective amount of netupitant or a pharmaceutically acceptable salt thereof and a therapeutically effective amount of palonosetron or a pharmaceutically acceptable salt thereof.

Ex. 1001, 23:8-15

U.S. Patent No. 9,186,357 (“the ‘357 Patent”)

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.

* * *

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.

* * *

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.

Ex. 1002, 21:48-51, 26:21-29, 26:45-48

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.

* * *

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.

* * *

24. The method of claim 19, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

Ex. 1002, 21:35-38, 22:62-23:10, 23:60-62

U.S. Patent No. 9,943,515 (“the ‘515 Patent”)

1. A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising 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, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration, wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.

Ex. 1003, 22:2-19

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 is effective to treat said nausea and vomiting for said five consecutive days.

* * *

19. The method of claim 11, wherein said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

Ex. 1003, 23:1-13, 24:15-18

U.S. Patent No. 10,828,297 (“the ‘297 Patent”)

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.

* * *

11. The method of claim 1, wherein said method prevents nausea in said subject.

Ex. 1004, 21:45-49, 22:20-21

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

* * *

22. The method of claim 3, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors seventy-two hours after said administration.

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.

Ex. 1004, 21:56-61, 22:65-23:3

Representative Claims Recite Improved Methods of Treating Cancer Patients

'826 Patent

The invention claimed is:

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 (NK₁) 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.

Ex. 1001, 21:39-63

'297 Patent

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

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.

Ex. 1004, 21:56-61, 23:1-3

As of November 2009, Patient Need for Better Nausea Treatments Remained

Petitioner's Lead "Herrstedt" Reference (Ex. 1010)

Anti-Emetic Therapy in Cancer Chemotherapy: Current Status

Jørn Herrstedt and Per Dombernowsky

Department of Oncology, Copenhagen University Hospital Herlev, Herlev, Denmark

(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 chemotherapy-induced nausea and vomiting will be given. The serotonin₃-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 neurokinin₁-receptor antagonists, has now been developed, and the first

* * *

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.

Ex. 1010, Abstract, 143

Petitioner's "Yeo" Reference (Ex. 1048)

[1]. 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, 534

Helsinn's Claimed Inventions Delivered Better Treatment for Chemotherapy-Induced Nausea

TABLE 6

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

Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No Nausea						
Overall	50.7	54.8	62.0	61.5	58.2	32
Acute	75.0	72.6	77.4	80.0	77.6	59
Delayed	53.7	59.3	65.0	68.1*	60.4	41
No Significant Nausea						
Overall	79.4	80.0	86.1	89.6*	85.8	56
Acute	93.4	94.1	94.2	98.5*	94.0	79
Delayed	80.9	81.5	89.8*	90.4*	88.1	59

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

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

Ex. 1001, 19-20



Eric Roeland, M.D.
FASCO, FAAHPM

“Table 6 of the ’826 patent 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) In contrast, *aprepitant-based triple therapy* administered to patients in Group 5 *did not* show a statistically significant improvement in “no nausea” or “no significant nausea” (pink highlights) compared to standard therapy.”

Ex. 2088 (-945), ¶ 260; Ex. 2089 (-946,-947), ¶ 247;
Ex. 2090 (-948), ¶ 244; Ex. 2091 (-949), ¶ 242

See, e.g., -945 POR (Paper 22), 65-66; -946 POR (Paper 23), 55-56;
-947 POR (Paper 23), 57-58; -948 POR (Paper 22), 60-61; -949 POR (Paper 23), 56-57

Azurity Failed to Substantiate the Motivation-to-Combine Theory Advanced in Its Petition

Exemplary Grounds Asserted by Azurity

'826 Patent (IPR2025-00945)	Ground 1	Claims 19, 22-23, 25	Obvious over MASCC and Hoffmann
	Ground 2	Claims 19-20, 22-23, 25	Obvious over MASCC and Bös
	Ground 3	Claims 19-23, 25	Obvious over MASCC , Bös , and ALOXI
	Ground 4	Claims 1-3, 8-10, 15-18, 24	Obvious over Herrstedt , Hoffmann , Hargreaves
	Ground 5	Claims 1-3, 6-10, 15-18, 24	Obvious over Herrstedt , Bös , and Hargreaves
	Ground 6	Claims 4-5	Obvious over Herrstedt , Bös , Hargreaves, and Herrington
	Ground 7	Claims 10-14	Obvious over Herrstedt , Bös , Hargreaves, and ALOXI

'297 Patent (IPR2025-00949)	Ground 1	Claims 1-4, 8-13, 17-19, 23	Obvious over Herrstedt and Bös
	Ground 2	Claims 5-6, 14-15, 20-21	Obvious over Herrstedt , Bös , and ALOXI
	Ground 3	Claims 7, 16, 21	Obvious over Herrstedt , Bös , and Hargreaves

**Every ground includes MASCC/Herrstedt as the primary reference
with Hoffmann/Bös as the main secondary reference**

Primary References (MASCC/Herrstedt) Disclose Aprepitant-Based Therapy

Azurity's Petition

A. MASCC

MASCC promulgates formal antiemetic recommendations of a multinational professional association on supportive care for cancer, updating the standard of care to the 2006 state-of-the-art. EX1013, 20.

* * *

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

-945 Petition (Paper 2), 10-11

Azurity's Petition

E. Herrstedt

Herrstedt, a 2007 journal article, summarizes 2007 CINV treatments, including antiemetic therapy with serotonin-receptor 5-HT₃ antagonists (e.g., palonosetron) and NK₁ antagonists (e.g., aprepitant). EX1010, Abstract. Herrstedt teaches adding a NK₁ antagonist to an antiemetic combination of 5-HT₃ antagonist plus corticosteroid (e.g., dexamethasone). *Id.* ("Aprepitant increases the effect... against acute emesis induced by" HEC or MEC). *Id.* Herrstedt teaches antiemetic

-945 Petition (Paper 2), 14-15; -946 Petition (Paper 2), 10-11; -947 Petition (Paper 2), 10-11; -948 Petition (Paper 2), 11-12; -949 Petition (Paper 2), 11-12

Neither MASCC nor Herrstedt disclose netupitant, let alone suggest substituting netupitant into the aprepitant-based "2006 state-of-the-art" treatment protocol

Secondary References (Bös/Hoffmann)

Disclose a Number of Molecules, Including Netupitant

Bös (Issued October 2001)

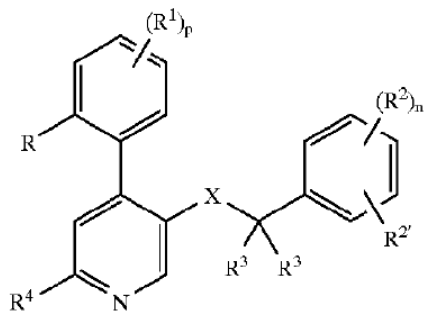
(57)

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.

SUMMARY OF THE INVENTION

This invention relates to compounds of the general formula

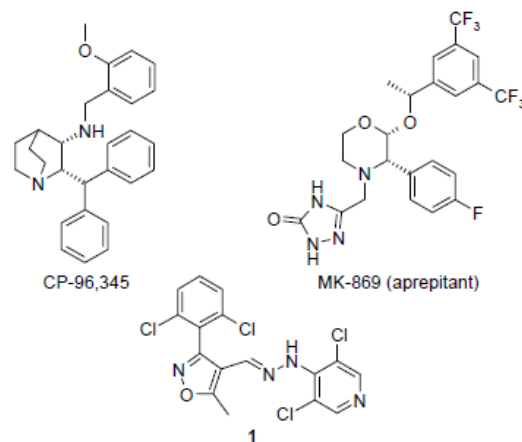


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Ex. 1011, Abstract, 2:1-15

Hoffmann (Published December 2005)

substance P.¹ Following the discovery of the first non-peptide NK₁ receptor antagonist CP-96,345 in 1991,² a remarkable number of small molecule NK₁ receptor antagonists were identified by many pharmaceutical companies in the last decade.³



Ex. 1014, 1362

Bös and Hoffmann predate MASCC/Herrstedt's aprepitant-based therapy, and do not describe substituting netupitant for aprepitant in a three-drug treatment protocol

Hoffmann Does Not Teach Treating Chemotherapy-Induced Nausea and Vomiting with Netupitant, or Netupitant as an Aprepitant-Replacement

Azurity

as the 5-HT₃ antagonist as MASCC recommended. Hoffmann suggesting substituting netupitant for the older aprepitant due to netupitant’s improved profile.

-945 Petition (Paper 2), 22

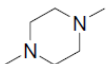
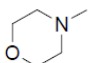
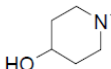
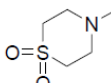
would lead to the erroneous ‘constricted analysis’ that KSR criticized.”). That a POSA could also pursue a quadruple (or more) therapy with all the additional costs and risk does not detract from the simple substitution that Hoffmann suggested.

-945 Reply (Paper 26), 16

Netupitant undifferentiated—better and worse in identified metrics

Hoffmann (Ex. 1011)

mood disorders such as anxiety and depression.⁴ MK-869 (aprepitant) was the first NK₁ 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

Compound	NR ¹ R 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

Ex. 1011, 1362, 1364

See, e.g., -945 POR (Paper 22), 29-31; -946 POR (Paper 23), 24-26;
-947 POR (Paper 23), 24-26; -948 POR (Paper 22), 28-30; -949 POR (Paper 23), 25-27

Bös Has Generic Teachings Regarding a Class of Molecules, and Does Not Suggest Replacing Aprepitant with any Compound


US06297375B1

(12) United States Patent
Bös et al.

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

(*) 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

(56) References Cited

U.S. PATENT DOCUMENTS

5,387,295	2/1995	Mills et al.	514/357
5,554,633	9/1996	Todd	514/357
5,612,337	3/1997	Baker et al.	514/236.2
5,719,147	2/1998	Doss et al.	514/227.5
5,972,508	10/1999	Repiak et al.	514/236.2

FOREIGN PATENT DOCUMENTS

089 765	9/1983	(EP)	
0285663	2/1987	(EP)	
0 235 663	9/1987	(EP)	
330 547	3/1990	(EP)	
038350	9/1990	(EP)	

OTHER PUBLICATIONS

Chem. Pharm. Bull. Tsuru et al. 45(10) p. 1642-1652 (1997);
J. Med. Chem. Natsugari et al., 38(10) pp. 3106-3120 (1995);
Barker, Reviews in the Neurosciences, vol. 7, No. 3, pp. 187-214 (1996);
Longmore, et al., Neurokinin-Receptor Antagonists: Pharmacological Tools and Therapeutic Drugs, Can. J. Physiol.

60 Abstract corresponding to WO 98/21185.
Abstract corresponding to WO 94/27604.
Abstract corresponding to WO 96/00213.
* cited by examiner

Primary Examiner—Makand 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-phenylpyridine derivatives connected by a bridge containing oxygen or nitrogen to a phenyl derivative.

65 Claims, No Drawings

Azurity Pharmaceuticals, Inc. EXHIBIT - 1014

Bös (Ex. 1014)

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 of 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 of the gut including ulcerative colitis and Crohn's disease, ocular injury and ocular inflammatory diseases.

The compounds of formula I are further useful for the treatment of motion sickness and emesis.

Ex. 1014, 3:64-4:24

Azurity Was Obligated to Prove That a POSA *Would Have* Been Motivated to Substitute Netupitant for Aprepitant—Not Just That a POSA Could Have

VIRTEK VISION INTERNATIONAL
ULC, Appellant
v.
ASSEMBLY GUIDANCE SYSTEMS,
INC., DBA Aligned Vision,
Cross-Appellant
United States Court of Appeals,
Federal Circuit.
Decided: March 27, 2024

[5] We conclude that the Board erred as a matter of law with regard to the motivation to combine. It does not suffice to meet the motivation to combine requirement to recognize that two alternative arrangements such as an angular direction system using a single camera and a 3D coordinate system using two cameras were both known in the art. Briggs discloses a

* * *

[6] The mere fact that these possible arrangements existed in the prior art does not provide a reason that a skilled artisan would have substituted the one-camera angular direction system in Keitler and Bridges with the two-camera 3D coordinate system disclosed in Briggs. There was

97 F.4th 882, 886-87 (Fed. Cir. 2024)

LEO PHARMACEUTICAL
PRODUCTS, LTD.,
Appellant,
v.
Teresa Stanek REA, Acting Director,
United States Patent and Trademark
Office, Appellee.
United States Court of Appeals,
Federal Circuit.
Aug. 12, 2013.

Moreover, because neither Dikstein nor Serup recognized or disclosed the stability problem, the record shows no reason for one of ordinary skill in the art to attempt to improve upon either Dikstein or Serup using Turi. The ordinary artisan would first have needed to recognize the problem, i.e., that the formulations disclosed in Dikstein and Serup were not storage stable. To discover this problem, the ordinary artisan would have needed to spend several months running storage stability tests. See '013 patent col. 10, l. 50–col. 11, l. 56; see also J.A. 545, 563–68. Only after recognizing the existence of the problem would an artisan then turn to the prior art and attempt to develop a new formulation for storage stability. If these discoveries

726 F.3d 1346, 1354 (Fed. Cir. 2013)

Azurity's Asserted Motivation to Combine: A POSA Would Have Believed Netupitant to Be an "Improved Drug[]"

Azurity's Petition

as the 5-HT₃ antagonist as MASCC recommended. Hoffmann suggesting
substituting netupitant for the older aprepitant due to netupitant's improved profile.

EX1009, ¶¶157-61; cf. EX1051 (reporting Helsinn's in-licensing of netupitant for

* * *

Bös provides ample reason to replace MASCC's aprepitant with Bös' new, improved netupitant. Indeed, MASCC suggested new species in the same class,

* * *

Hoffmann teaches netupitant is an improved NK₁ antagonist. EX1011, Abstract, 1364. A POSA would have known to try an improved NK₁ antagonist (netupitant) instead of aprepitant in Herrstedt's combination. EX1009, ¶247.

* * *

A POSA also had reason to modify Herrstedt's triple therapy to include the improved NK₁ antagonist, netupitant. The POSA would have sought the enhanced efficacy of Herrstedt's antiemetic combination with new, improved drugs targeting the same mechanistic pathway—NK₁-receptor antagonism. As Hoffmann explains,

See, e.g., -945 Petition (Paper 2), 22, 25, 32, 51

Azurity's Reply

understood, "the problem [is] treating CINV[.]" ID, 25. Indeed, a POSA would

have substituted netupitant as the NK₁-inhibitor for the same reason the art

substituted palonosetron for ondansetron (the 5-HT₃-inhibitor): to "enhance[] the

efficacy of [the existing] combination with new, improved drugs targeting the

same mechanistic pathways." Pet. 50. Helsinn vaguely argues that netupitant and

See, e.g., -945 Reply (Paper 26), 14

The Experts Agree That Superiority, or at Least Equivalency, Would Have Been Required



Dr. Peroutka

Q. You would agree with me that a ***POSA would not be changing the aprepitant triple therapy*** unless they believe that the change would provide similar or better patient outcomes, correct?

A. *Correct.*

Ex. 2086, 294:4-10



Dr. Roeland

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.***

Ex. 2088 (-945), ¶ 219; Ex. 2089 (-946, -947), ¶ 205;
Ex. 2090 (-948), ¶ 203; Ex. 2091 (-949), ¶ 202

Azurity Did Not Show That a POSA Would Have Believed Netupitant to Be a “New, Improved Drug[],” as Compared to Aprepitant



Dr. Peroutka

Q. Did you evaluate any data comparing aprepitant and netupitant that's in the prior art?

A. Let me think about that a little bit. Specific data, some of the tables may – in the back here might have data, *but not in the prior art*.

Ex. 2086, 243:10-16

Q. And you haven't compared the molecules casopitant, netupitant, and aprepitant in terms of the molecular structural properties, correct?

A. Yes. That's *beyond on the scope*. I'm not a medicinal chemist.

Ex. 2086, 253:13-18

Q. Do you have any data whatsoever to determine the comparison of affinity between aprepitant and netupitant in the prior art?

A. It was *out of scope*. I didn't look it up.

Ex. 2086, 242:25-243:5

Q. So let's be clear. You did not analyze the affinity between casopitant, netupitant, and aprepitant for the NK-1 receptor, right?

A. *Correct*.

Ex. 2086, 254:12-17

Dr. Peroutka's Later Concessions Undermine the Initial Institution Analysis

Institution Decision

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 NK₁ 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 ID (Paper 12), 26

1. **“Petitioner’s reason for substitut[ion]” was unproven assertion that netupitant was an “improved drug”**
2. **“Equivalency” not proven where comparison between netupitant and aprepitant was “outside the scope” of Dr. Peroutka’s analysis**

On Reply, Azurity renounces any claim of having proven equivalency (see -945 Reply (Paper 22), 14-15 (not challenging Helsinn’s “argu[ment] that netupitant and aprepitant were not ‘equivalent’”))

Dr. Roeland Confirmed the Full Record Does Not Support the ID's Analysis



Dr. Roeland

“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

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.)”

Ex. 2088 (-945), ¶¶ 222-24

Recognizing Its Evidentiary Failures, Azurity Attempts to Walk Away from Its Own Petition's Motivation Theories

Petition: Reliant upon “improve[ment]”

as the 5-HT₃ antagonist as MASCC recommended Hoffmann suggesting substituting netupitant for the older aprepitant due to netupitant's improved profile. EX1009, ¶¶157-61; cf. EX1051 (reporting Helsinn's in-licensing of netupitant for

* * *

Bös provides ample reason to replace MASCC's aprepitant with Bös' new, improved netupitant. Indeed, MASCC suggested new species in the same class,

* * *

Hoffmann teaches netupitant is an improved NK₁ antagonist. EX1011, Abstract, 1364. A POSA would have known to try an improved NK₁ antagonist (netupitant) instead of aprepitant in Herrstedt's combination. EX1009, ¶247.

* * *

A POSA also had reason to modify Herrstedt's triple therapy to include the improved NK₁ antagonist, netupitant. The POSA would have sought the enhanced efficacy of Herrstedt's antiemetic combination with new, improved drugs targeting the same mechanistic pathway—NK₁-receptor antagonism. As Hoffmann explains,

See, e.g., -945 Petition (Paper 2), 22, 25, 32, 51

Reply: Improvement not Required

E. Better outcome is not the standard

Helsinn similarly invites error by requiring that substituting netupitant for aprepitant would result in better clinical outcomes (POR 35) but, again, this is not the law. *Bayer*, 874 F.3d at 1328 (“[O]bviousness 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.” (original emphasis) (cleaned up)). Moreover, Helsinn

See, e.g., -945 Reply (Paper 26), 16-17

See, e.g., -945 Sur-Reply (Paper 30), 1-10; -946 Sur-Reply (Paper 31), 1-10;
-947 Sur-Reply (Paper 31), 1-10; -948 Sur-Reply (Paper 30), 1-10; -949 Sur-Reply (Paper 31), 1-10

Bayer Does Not Absolve Azurity from Needing to Prove the Motivation That Azurity Put Forward



InTOUCH TECHNOLOGIES, INC.,
doing business as InTouch Health,
Plaintiff-Appellant,

v.

VGO COMMUNICATIONS, INC.,
Defendant-Appellee.

United States Court of Appeals,
Federal Circuit.

May 9, 2014.

Intouch Techs., Inc. v. VGO Comm's. Inc.,
751 F.3d 1327, 1351 (Fed. Cir. 2014)

[30, 31] Even assuming Dudenhoeffer disclosed the type of “arbitrator” claimed in the patent before us, there is insufficient evidence on this record of a reason or motivation for one of ordinary skill in the art at the time of the invention to combine Dudenhoeffer with Jouppi and Roach. A reason for combining disparate prior art references is a critical component of an obviousness analysis; “this analysis should be made explicit.” *KSR*, 550 U.S. at 418, 127 S.Ct. 1727 (arguments need to provide an “articulated reasoning with some rational underpinning” to make the asserted combinations) (quoting *In re Kahn*, 441 F.3d at 988.). “[I]t can be important to

Azurity’s obviousness theories fail because Azurity has not proven its proffered motivation to combine (*i.e.*, netupitant’s superiority), not due to a failure to prove netupitant was the “best” option available to a POSA

Nor Has Azurity Substantiated the Undeveloped, Conclusory “Obvious-to-Try” Allegation in its -945 Petition

Azurity’s Petition

C. Obvious to Combine and Reasonably Expect Success

The combination of MASCC’s 3-drug combination substituting netupitant and palonosetron would have been obvious to try and reasonably expect success as explained in §X.E above. Adding the FDA-approved ALOXI label bolsters the

-945 Petition (Paper 2), 31

Azurity’s Reply

G. Hoffmann and Bös narrowed the NK₁-inhibitors to try

Helsinn argues that the prior-art NK₁-inhibitors were not “finite, small, or easily traversed” in 2009. POR 53. Yet Hoffmann highlighted two out of 31. EX1011, 1362. Bös highlighted three out of “millions.” EX1014, 13:14-23:16 (compounds Ia-Ic). Both identified netupitant as a preferred candidate. While

See, e.g., -945 Reply (Paper 26), 19

Azurity's Obvious-to-Try Conclusion Still Requires a Motivation to Combine



Virtek Vision

invention would have been obvious. In *KSR*, the Supreme Court explained, “[w]hen there is a design need or market pressure to solve a problem and there are a finite number of identified, predictable solutions, a person of ordinary skill has good reason to pursue the known options within his or her technical grasp.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421, 127 S.Ct. 1727, 167 L.Ed.2d 705 (2007). “If *KSR* did not do away with the requirement that there must exist a motivation to combine various prior art references in order for a skilled artisan to make the claimed invention.

Virtek Vision Int’l ULC v. Assembly Guidance Sys.,
97 F.4th 882, 887 (Fed. Cir. 2024)

Azurity

G. Hoffmann and Bös narrowed the NK₁-inhibitors to try

Helsinn argues that the prior-art NK₁-inhibitors were not “finite, small, or easily traversed” in 2009. POR 53. Yet Hoffmann highlighted two out of 31. EX1011, 1362. Bös highlighted three out of “millions.” EX1014, 13:14-23:16 (compounds Ia-Ic). Both identified netupitant as a preferred candidate. While Helsinn and Dr. Roeland exaggerate the challenge, Hoffmann and Bös provide ample direction to those seeking an NK₁-inhibitor to employ instead of aprepitant.

See, e.g., -945 Reply (Paper 26), 19

Regardless, the Number of Available NK₁ Inhibitors Further Defeats Any Obvious-to-Try Allegation



Dr. Peroutka

Q. [I]t's your opinion that a scientist would evaluate the *other NK-1 receptor antagonists* that were known as of 2009, correct?

A. *Yes.* It's a reasonable thing to do.

Ex. 2086, 84:15-18

Hoffmann 2005 (Ex. 1011)

Neurokinin (NK) receptors belong to the family of G-protein coupled receptors and can be divided into three subtypes: NK₁, NK₂ and NK₃. The endogenous ligand for NK₁ receptors is the 11 amino acid neuropeptide substance P.¹ Following the discovery of the first non-peptide NK₁ receptor antagonist CP-96,345 in 1991,² a remarkable number of small molecule NK₁ receptor antagonists were identified by many pharmaceutical companies in the last decade.³

Ex. 1011, 1362

MacCoss 2004 (Ex. 2096)

sea and vomiting. Based on our experiences and knowing the large number of other companies working in this area, it is very likely that tens of thousands of 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

Ex. 2096, 1812-13

Dr. Peroutka's Ignoring Available NK₁ Inhibitors based on Hindsight Does Not Support Obviousness-to-Try



Dr. Peroutka

Q. Is it correct that *the only NK-1 receptor antagonists that you evaluated* were aprepitant, fosaprepitant, netupitant, and casopitant?

A. Yes.

Q. And aprepitant, fosaprepitant, and casopitant had human data, correct?

A. I believe so, yeah.

Ex. 2086, 122:20-123:7

* * *

Q. Wh[y] was the only NK-1 receptor antagonist that you evaluated that didn't have human data netupitant?

A. That was – that was the *subject of this patent dispute*.

Ex. 2086, 127:5-10

Focus on Netupitant Because It Is “subject of this patent dispute” Cannot Support Obviousness



MONARCH KNITTING MACHINERY
CORP. Declaratory Judgment Plain-
tiff/Counterclaim Plaintiff-Appellee,

v.

SULZER MORAT GMBH, Declaratory
Judgment Defendant-Appellant,

United States Court of Appeals,
Federal Circuit.

March 10, 1998.

139 F.3d 877, 881 (Fed. Cir. 1998)

the stem segment. Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness. See, e.g., *In re Antle*, 58 C.C.P.A. 1382, 444 F.2d 1168, 1171–72, 170 USPQ 285, 287–88 (CCPA 1971) (warning against selection of prior art with hindsight).



INSITE VISION INCORPORATED, In-
spire Pharmaceuticals, Inc., Pfizer
Inc., Plaintiffs-Appellees

v.

SANDOZ, INC., Defendant-Appellant

United States Court of Appeals,
Federal Circuit.

April 9, 2015.

783 F.3d 853, 859 (Fed. Cir. 2015)

2009). “In considering motivation in the obviousness analysis, the problem examined is not the specific problem solved by the invention.” *In re Kahn*, 441 F.3d 977, 988 (Fed.Cir.2006). “Defining the problem in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.” *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed.Cir.1998). And,

**Azurity Does Not Meaningfully Contend That It Has
Proven Obviousness When Applying the Correct Legal Analysis**

Identifying the Problem Facing a POSA Guards Against Hindsight in the Motivation-to-Combine Analysis



WBIP, LLC, Plaintiff-Cross-Appellant,

v.

KOHLER CO., Defendant-Appellant.

United States Court of Appeals,
Federal Circuit.

Decided: July 19, 2016

Too often the obviousness analysis is framed as an inquiry into whether a person of skill, with two (and only two) references sitting on the table in front of him, would have been motivated to combine (or, in Kohler's view, could have combined) the references in a way that renders the claimed invention obvious. The real question is whether that skilled artisan would have plucked one reference out of the sea of prior art (Phipps) and combined it with conventional coolant elements to address some need present in the field (the need for low-carbon monoxide emission marine gen-sets). Whether a skilled artisan would

829 F.3d 1317, 1337 (Fed. Cir. 2016)

The Properly Defined Problem Facing a POSA Is a Factual Question



**INSITE VISION INCORPORATED, In-
spire Pharmaceuticals, Inc., Pfizer
Inc., Plaintiffs–Appellees**

v.

SANDOZ, INC., Defendant–Appellant

United States Court of Appeals,
Federal Circuit.

April 9, 2015.

Plaintiffs respond that identifying the problem faced by a person of skill in the art is a factual question, on which the district court properly ruled. Plaintiffs

* * *

The district court did not clearly err in framing the obviousness inquiry as it did, based on its understanding of the problem facing those skilled in the art at the time the invention was made. Moreover, the district court, in framing the question, did not foreclose Sandoz from attempting to prove that the claims would have been obvious based on the treatment of conjunctivitis by the topical administration of azithromycin.

783 F.3d 853, 859 (Fed. Cir. 2015)

Azurity's Expert Had Not Identified a Problem with Aprepitant Therapy, and Was Not Familiar with the Required Analysis



Dr. Peroutka

Q. From your perspective, was a POSA faced with any problem in treating chemotherapy-induced nausea and vomiting as of 2009?

A. You have to define problem. That's where the – our – your words are not making sense to me, in the sense that, you know, problem to be solved, I'm just not understanding what you mean by that.

Ex. 2086, 108:4-10

* * *

Q. What was the goal of what a POSA was trying to do in 2009?

A. Well, to me, a POSA has the skill set that could do things. And in this case, could a POSA – a POSA would be needed to review the state of – the standard of care, to review the research articles and then *iterate with the claims* to see if it was obvious in a legal sense.

Ex. 2086, 108:11-18

Azurity Misreads *Cytiva* in Looking to Sidestep the Problem-Facing-a-POSA Analysis

Azurity

nausea and vomiting. By Helsinn’s logic, Hoffmann’s praise for netupitant in the context of treating CINV (EX1011, 1362; ID 26-27) was a futile gesture because a POSA would never have paid attention given all the other alternatives. Fortunately, neither the law nor the art are so blinkered. *Cytiva Bioprocess R&D AB v. JSR Corp.*, 122 F.4th 876, 884 (Fed. Cir. 2024) (“To require a separate justification for starting with Domain C, when that starting point is already taught in the prior art, would lead to the erroneous ‘constricted analysis’ that *KSR* criticized.”). That a

See, e.g., -945 Reply (Paper 26), 16

Cytiva



sis in original). For example, Abrahmsén states: “According to still another aspect of the invention there is provided for a recombinant DNA fragment coding for any of the E D A B C domains of staphylococcal protein A, wherein the glycine codon(s) in the Asn-Gly coding constellation has been replaced by an alanine codon.” J.A. 3833 col. 2 ll. 32–37. This teaching expressly discloses the proposed G29A modification to Domain C—i.e., what is claimed in the challenged patents. To require a sepa-

122 F.4th 876, 884-85 (Fed. Cir. 2024)

No reference taught substituting netupitant into triple therapy, and Azurity therefore needed to show a problem that would have motivated a POSA to make Azurity’s desired substitution

Azurity's Reply Does Not Purport to Have Proven Obviousness When the Properly Defined Problem Facing a POSA Is Applied

Azurity's Reply

B. Nausea was not the only problem confronting the POSA

Helsinn reimagines the problem to be solved as treating nausea rather than treating CINV. E.g., POR 2 (“Azurity ignored the problem of chemotherapy-induced nausea[.]”). Obviousness is not limited to the inventor’s problem. *KSR Int’l v. Teleflex Inc.*, 550 U.S. 398, 420 (2007) (“any need or problem known in the field”). Regardless, Helsinn itself defined the field broadly as “the use of centrally

See, e.g., -945 Reply (Paper 26), 13

Problem Was Need for Better Nausea Treatments

Herrstedt 2007 (Ex. 1010)

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.

* * *

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. It should be noted that the doses of anti-emetics are defined in studies using emesis as the primary end-point. It is therefore unknown if higher doses than recommended of for example corticosteroids increase the effect against nausea.

Ex. 1010, 143, 148

Yeo (Ex. 1048)

[1]. 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, 534

Expert Testimony Supports Only Helsinn's Identification of the Problem Facing a POSA



Dr. Roeland

“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).”

“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.*”

Ex. 2088 (-945), ¶¶ 72, 208

Undisputed Expert Testimony Showed That a POSA Would Have Explored a Variety of Approaches to Develop an Anti-Nausea Treatment



Dr. Roeland

“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.)

Ex. 2088 (-945), ¶ 73

A POSA Would Have Looked to Olanzapine



Dr. Peroutka

Q. So olanzapine is something that a POSA *would have considered* modifying existing triple therapy in 2009 to help patients with chemotherapy-induced nausea and vomiting, correct?

A. It's possible.

Q. But you didn't evaluate that for the purposes of your opinions in this case?

A. Correct.

Ex. 2086, 134:11-21

A POSA Would Have Looked to Gabapentin



Dr. Peroutka

Q. And *gabapentin* is another agent that would have been considered as a potential for modifying existing triple therapy for treating patients with chemotherapy-induced nausea or vomiting, correct?

A. I would say *it's a possibility*, but not all POSAs would have thought that.

Ex. 2086, 134:23-135:4



Dr. Roeland

“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.)”

Ex. 2088 (-945), ¶ 97

A POSA Would Have Looked to Cannabinoids



Dr. Peroutka

Q. You will agree with me that *cannabinoids* w[ere] something that a *POSA would consider* as a potential for modifying existing triple therapy to help patients with chemotherapy-induced nausea, correct?

A. It was a potential thing to consider.

Q. But you did not do that as part of your declaration in this case, correct?

A. Correct.

Ex. 2086, 136:15-137:1

Agenda

- Serial motivation failures defeat every ground
- Failure to show a reasonable expectation of success
- Objective indicia confirm nonobviousness
- Failure to show that the prior art discloses every claim limitation

Reasonable Expectation of Success Requires Expectation of Achieving Claimed Patient Benefits, Not Merely Administering Netupitant



JANSSEN PHARMACEUTICALS,
INC., Janssen Pharmaceutica
NV, Plaintiffs-Appellees

v.

TEVA PHARMACEUTICALS USA,
INC., Defendant-Appellant

United States Court of Appeals,
Federal Circuit.

Decided: July 8, 2025

[14, 15] “The reasonable expectation of success requirement refers to the likelihood of success in combining references to meet the limitations of the claimed invention.” *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016). But the district court

141 F.4th 1367, 1383 (Fed. Cir. 2025)

Azurity has failed to show that a POSA would have reasonably expected to successfully achieve, at least:

- 1** Claimed superiority of netupitant-based therapy ('826 patent)
- 2 Claimed treatment of nausea provided by netupitant, alone ('297 and '515 patents)
- 3 Claimed treatment of nausea provided by the combination of netupitant and palonosetron ('357 patent)

Exemplary Claimed Invention of the '826 Patent—the Standard for “Success”

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 (NK₁) 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.

1. Treatment of “both nausea and vomiting” in a patient”

2. Through administration of netupitant, palonosetron, and dexamethasone

3. Providing superior treatment of “both nausea and vomiting” than palonosetron / dexamethasone (without netupitant)

Ex. 1001, 21:39-63

Claim Construction

Plain Language of Claim 1 Requires Treating “both” (1) Nausea and (2) Vomiting

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 (NK₁) 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.

1. Treatment of “both nausea and vomiting” in a patient”

2. Through administration of netupitant, palonosetron, and dexamethasone

3. Providing superior treatment of “both nausea and vomiting” than palonosetron / dexamethasone (without netupitant)

Ex. 1001, 21:39-63

Helsinn Explained—and Azurity Has Not Disputed—that the Preamble Is Limiting

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

Helsinn's POR

A claim preamble is limiting when “other parts of the patent’s claims rely on predicates in the preamble, or when the preamble is otherwise necessary to give life, meaning, and vitality to the claim language.” *In re Xencor, Inc.*, 130 F.4th 1350, 1358 (Fed. Cir. 2025). ***Here, the preambles of claims 1 and 19 meet both criteria and should be considered limiting . . .*** The preambles of claims 1 and 19 recite treatment of both nausea and vomiting in a patient or human subject “in need thereof,” and such language can be limiting. *See Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1332-34 (Fed. Cir. 2003). Here, in the body of the claims, the ***steps of the recited method for treating both nausea and vomiting are performed on the patient or subject who is described in the preamble*** as needing such treatment.

-945 POR (Paper 22), 16-17

Ordinary Meaning of “treat[ing] both nausea and vomiting” Requires Treatment of “both” Distinct Afflictions



Dr. Peroutka

Q. You will agree with me that *nausea is different than vomiting*, correct?

A. Correct.

Ex. 2086, 38:22-24

* * *

Q. Okay. And treatments that work for vomiting may not necessarily work for nausea. Is that accurate?

A. It's possible.

Ex. 2086, 42:2-5



Dr. Roeland

“Nausea and vomiting each constitute *a separate and distinct adverse event* caused by cancer treatment Nausea and vomiting do not always coexist simultaneously, as one can experience nausea without vomiting, and one can also suddenly vomit without nausea.”

Ex. 2088 (-945), ¶¶ 32-33

Azurity Improperly Requests to Rewrite the Claim's Recitation of “treat[ing] both nausea and vomiting”

Azurity's Reply

2. Claim 1 recites “both” not “each of”

Moreover, Azurity does not concede that treating “both nausea and vomiting” to a greater extent means treating *each of* nausea and vomiting to a greater extent. Helsinn’s both-and drafting explicitly joins nausea and vomiting together for the greater-extent comparison. Helsinn could have used a narrower each-of construction, but did not, and does not provide an intrinsic basis for its narrower reading of this plain language. Thus, a net improvement for these parameters together meets claim 1. Record evidence confirms that combining 5-

See, e.g., -945 Reply (Paper 26), 4

Azurity's Interpretation

1. A method of treating ~~both~~ ^{and/or} nausea ~~and~~ vomiting for five consecutive days in a patient in need thereof, comprising:

Azurity's “net improvement” reading would permit *worsening* of nausea

Claim 1 Further Recites a Method of “treat[ing] both nausea and vomiting” to a “greater extent” than an Identified Comparator

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 (NK₁) 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.

1. Treatment of “both nausea and vomiting” in a patient”

2. Through administration of netupitant, palonosetron, and dexamethasone

3. Providing superior treatment of “both nausea and vomiting” than palonosetron / dexamethasone (without netupitant)

Ex. 1001, 21:39-63

See, e.g., -945 POR (Paper 22), 16-20; -945 Sur-Reply (Paper 30), 10-13

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 51

Experts Agree That Statistical Significance Is How a POSA Would Understand the Claimed Treatment Superiority Is “Real”



Dr. Peroutka

Q. Statistics help us figure out if an *effect* we are seeing from a clinical study is actually real or if it could be due to chance, correct?

A. So statistics are, as you said, Mr. Ashkenazi, designed to show the likelihood that the effect [that] is observed is, quote, *real*

Ex. 2086, 22:17-23:15

* * *

Q. Okay. And scientists understand that in order to determine whether an *effect is real* or potentially due to random chance, we use statistics to make that determination, correct?

A. *Yes.* But it varies on the importance based on the primary versus secondary versus exploratory endpoints.

Ex. 2086, 24:9-16

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.

“effect” recited
in claim

Ex. 1001, 21:39-63

Specification Confirms That Statistical Significance Is Required

Claim 1

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.

Ex. 1001, 21:39-63

'826 Patent Specification

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.

Ex. 1001, 8:24-34

“[M]easurable result” (treating both nausea and vomiting) must be “evaluated based upon its statistical significance relative to [the] baseline” of palonosetron / dexamethasone treatment

Azurity Failed to Show that a POSA Would Have Reasonably Expected to Successfully Practice the Claimed Method

Petition Argued a Reasonable Expectation of Success Based on “Complete Response” Rates with Aprepitant Therapy

Azurity’s Petition

L. Obvious to Combine and Reasonably Expect Success

By the critical date, a POSA had good reason to treat acute and delayed CINV following MEC or HEC with Herrstedt’s triple-antiemetic combination therapy, substituting new, improved NK₁ and 5-HT₃ antagonists. Herrstedt describes the three-drug combination administered on day 1 yielded superior response rates (complete response) compared to the combination lacking NK₁ antagonist. EX1010, 146 (“Again a statistical[] benefit favouring aprepitant was seen, resulting in a complete response in the aprepitant arm of 72.0% versus 60.6% in the control arm (P = 0.003).”); EX1009, ¶¶333-39. The POSA would have

See, e.g., -945 Petition (Paper 2), 50

Azurity’s Petition

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

Herrstedt teaches the triple therapy (with a NK₁ antagonist) is a more effective than without. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin,’ was the primary end-point in all studies. Two of the HEC studies used an identical design comparing *ondansetron* [5-HT₃ antagonist], *dexamethasone* [corticosteroid], and *placebo* day 1 followed by dexamethasone plus placebo days 2-4 with *ondansetron*, *dexamethasone* and *aprepitant* [NK₁ antagonist] day 1 followed by dexamethasone days 2-4 plus aprepitant days 2-3. In the Hesketh study, a complete response of 72.7% in the aprepitant arm versus 52.3% in the control arm was seen, and in the Poli-Bigelli study complete response rates were 62.7% versus 43.3%. The most recently

See, e.g., -945 Petition (Paper 2), 42

As an Initial Matter, Azurity Has Not Justified Its Wholesale Reliance on Aprepitant Data



Dr. Peroutka

Q. For the NK-1 receptor antagonist[s] discussed in Hoffmann and Bös, you – you have not provided any comparison of the propert[ies] of those compounds with aprepitant other than to say they are considered NK-1 receptor antagonists, right?

A. I have not provided that analysis.

Ex. 2086, 281:11-18

Q. And you evaluated the difference between netupitant and aprepitant with respect to bioavailability in your declaration?

A. No.

Ex. 2086, 240:25-241:3

Q. And you haven't analyzed how casopitant, netupitant, or aprepitant bind with the NK-1 receptor antagonist, correct?

A. That was not in the scope.

Ex. 2086, 253:20-24

“Complete Response” Fails to Show Reasonable Expectation of Success in Treating “both nausea and vomiting,” as Claimed



Dr. Roeland

“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.*”

Ex. 2088 (-945), ¶ 53

Azurity’s Reply

1373 As Helsinn’s Dr. Roeland explained, these are the gold-standard measurements of nausea and vomiting available. EX2088, ¶¶ 46-47 (“[S]ponsors 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, e.g., -945 Reply (Paper 26), 4; -946 Reply (Paper 27), 2-3; -947 Reply (Paper 27), 2-3; -948 Reply (Paper 26), 2-3; -949 Reply (Paper 27), 2-3

- Azurity endorses Dr. Roeland’s analysis of the “complete response” endpoint

Azurity's Expert Alleged that Four Aprepitant Studies Support an Expectation of Treating Nausea; None Does



Dr. Peroutka

Q. The four [studies] that you rely upon to say that aprepitant can treat nausea are *the two that are included in the FDA label, Campos, and Herrington*. Is that accurate?

A. Yes, those are the four main [studies].

Ex. 2086, 249:11-17

FDA Label: Aprepitant Therapy Failed to Provide a Statistically Significant Improvement in “both” Nausea and Vomiting

FDA-Approved Label for EMEND® (Ex. 1030)

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**

Table 2

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

No Nausea			
Overall	49	39	NS*
Delayed phase	53	40	NS*
No Significant Nausea			
Overall	71	64	NS**
Delayed phase	73	65	NS**

Treatment Regimens
Highly Emetogenic Chemotherapy Trials

Treatment Regimen	Day 1	Days 2 to 4
Aprepitant	Aprepitant 125 mg PO Dexamethasone 12 mg PO Ondansetron 32 mg I.V.	Aprepitant 80 mg PO Daily (Days 2 and 3 only) Dexamethasone 8 mg PO Daily (morning)
Standard Therapy	Dexamethasone 20 mg PO Ondansetron 32 mg I.V.	Dexamethasone 8 mg PO Daily (morning) Dexamethasone 8 mg PO Daily (evening)

Aprepitant placebo and dexamethasone placebo were used to maintain blinding.

See, e.g., -945 POR (Paper 22), 47-49; -945 Sur-Reply (Paper 30), 23; -946 POR (Paper 23), 42-45; -946 Sur-Reply (Paper 31), 22; -947 POR (Paper 23), 42-45; -947 Sur-Reply (Paper 31), 22; -948 POR (Paper 22), 46-49; -948 Sur-Reply (Paper 30), 22-23; -949 POR (Paper 23), 43-46; -949 Sur-Reply (Paper 31), 23

Dr. Peroutka Confirmed That the FDA-Approved EMEND® Label Does Not Show That Statistical Significance in the Treatment of Nausea



Dr. Peroutka

Q. [W]e are now in Exhibit 1030, the 2009 Emend label, Emend IV, you will see that there is a star and it says: “Not statistically significant when adjusted for multiple comparisons. Correct?

A. Correct.

Ex. 2086, 175:17-23

* * *

Q. You will agree with me that Merck and the FDA stated, when looking at the Poli-Bigelli study, the study that’s included in the 2003 label and the study that’s included in the 2008 label, both Tables 2, that *aprepitant did not show a statistically significant difference compared to standard therapy for no nausea, whether it’s overall or delayed*. Is that accurate?

A. That is *accurate*, statistically accurate.

Ex. 2086, 176:12-24

Dr. Peroutka Confirmed a POSA Would “Mainly” Rely upon the FDA-Approved Label for Aprepitant, Which Showed No Significant Effect Against Nausea



Dr. Peroutka

Q. What you’re relying upon are the netupitant studies that we reviewed, the four phase 3 clinical trials that you and I have discussed and Campos. Is that accurate?

A. *Mainly the two pivotals, because that’s what the FDA reviewed.*

* * *

Ex. 2086, 247:21-248:1

Q. [W]e’ve just reviewed the two pivotal studies that were included in the Emend label approved by the FDA, correct?

A. Correct

Q. And you will agree with me that in both Tables 1 and Tables 2 [of the Emend label], for no nausea and no significant nausea, aprepitant showed no statistical – statistically significant difference compared to standard therapy, correct?

A. Correct.

Ex. 2086, 180:21-181:1

Herrington: Treatment of Nausea “not different” with Aprepitant Therapy

Herrington 2008 (Ex. 1016)

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

* * *

TABLE 4
Severity of Nausea Using VAS

	Severity of nausea using VAS (mean±SD; median, range)			
	Arm A Palonosetron plus 3-day aprepitant, n = 26	Arm B Palonosetron plus 1-day aprepitant, n = 26	P*	Arm C Palonosetron plus placebo, n = 16
Day 1	12.6 ± 24.9 0(0-95)	8.7 ± 15.7 0(0-60)	.82	15.6 ± 32.1 0(0-95)
Day 2	15.2 ± 24.6 4(0-95)	11.0 ± 16.1 1(0-50)	.80	28.4 ± 39.2 2.5(0-100)
Day 3	15.0 ± 26.1 1.5(0-95)	12.3 ± 16.5 2.5(0-50)	.95	30.3 ± 40.4 2.5(0-100)
Day 4	10.5 ± 21.8 3.5(0-95)	16.6 ± 23.6 2.5(0-75)	.62	19.6 ± 31.5 2.5(0-95)
Day 5	12.0 ± 25.2 0(0-95)	18.3 ± 27.2 0(0-80)	.52	20.6 ± 34.0 0(0-95)

Herrington 2008 (Ex. 1016)

Other Efficacy Endpoints and Safety

The incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms (Table 4 and Fig. 2). In addition, the fre-

* * *

<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.¹⁶

Ex. 1016, Abstract, 2084, 2086

See, e.g., -945 POR (Paper 22), 49-51; -945 Sur-Reply (Paper 30), 23; -946 POR (Paper 23), 45-47; -946 Sur-Reply (Paper 31), 22; -947 POR (Paper 23), 45-47; -947 Sur-Reply (Paper 31), 22; -948 POR (Paper 22), 49-51; -948 Sur-Reply (Paper 30), 22-23; -949 POR (Paper 23), 46-48; -949 Sur-Reply (Paper 31), 23

Azurity Relies on a Single Reference as Allegedly Showing Aprepitant Having a Statistically Significant Effect against Nausea



Dr. Peroutka

Q. [L]et's make sure we're clear. For every study other than Campos, *the aprepitant regimen did not have a statistically significant difference for treating nausea or significant nausea* compared to the control in every study that we looked at, other than Campos. Is that accurate?

A. Yes, with the caveat in that sample size.

Ex. 2086, 228:15-24

Azurity's Petition

Helsinn alleged "aprepitant's effect was limited principally to vomiting, *not nausea*, and that aprepitant *did not provide as much benefit during the acute phase* [i.e., 0-24 hours] of CINV." EX1001, 2:12-15. Yet Campos discloses aprepitant's beneficial effect for *nausea* and shows it provided significant additive benefit during the acute phase of CINV. EX1009, ¶1352; EX1023, Abstract, 1763

-945 Petition (Paper 1), 63

“Campos” Does Not Support a Reasonable Expectation of Success

Dr. Roeland’s *unrebutted* testimony showed that a POSA would not have credited Campos 2001’s purported anti-nausea effects, including because:

1. Subsequent aprepitant literature and the FDA-approved label concluded aprepitant failed to impact nausea;
2. It relied on aprepitant doses nearly 5.5 times higher than the FDA-approved dosing regimen, which Dr. Peroutka agreed could *cause* nausea
3. Its results were dubious, (*e.g.*, reporting that no patient experienced significant nausea)
4. Its statistical analysis failed to account for false positives through multiplicity correction

Ex. 2088 (-945), ¶¶ 122-30; Ex. 2089 (-946, -947), ¶¶ 119-27;
Ex. 2090 (-948), ¶¶ 119-27; Ex. 2091 (-949), ¶¶ 119-27

Conceding Dr. Roeland’s analysis, Azurity’s Reply does not cite to Campos once

Dr. Peroutka Conceded that a POSA Would Recognize That the Doses of Aprepitant in Campos Could *Cause* Nausea



Dr. Peroutka

Q. You will agree with me that prior to [and following] treatment, *Campos gives 400 milligrams* of aprepitant orally and the *Emend label* has . . . only *one dosage of 125 milligrams*, correct?

A. Correct

Q. Now, you will agree with me that on days 2 through 5, *Campos gives 300 milligrams on each day*, and the *Emend label only gives 80 milligrams* on days 2 and 3, correct?

A. Correct.

Ex. 2086, 153:14-154:12

* * *

Q. [Y]ou would agree with me that 400 milligrams of orally given [aprepitant] . . . [pre and] post treatment on day 1, and 300 milligrams being given orally on days 2 through 5 *could have a concern to have a side effect of nausea?*

A. It could. As I state here, it could.

Ex. 2086, 158:16-24; *see also id.*, 155:9-13 (Dr. Peroutka agreeing that “higher amounts of aprepitant are known to have side effects of nausea”)

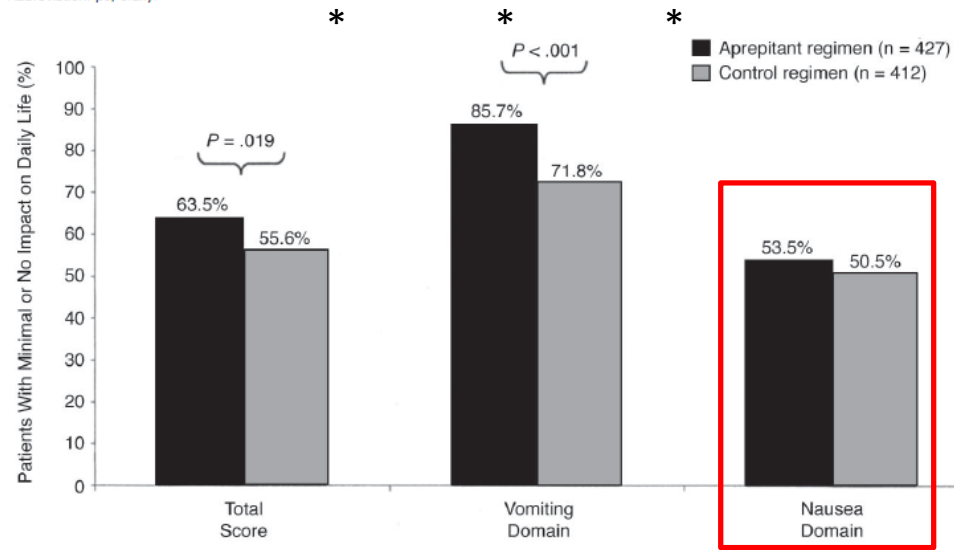
Azurity's Literature Reiterated That Aprepitant Therapy Did Not Provide a Statistically Significant Improvement in Nausea

Warr 2005 (Ex. 1034)

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.



Warr 2005 (Ex. 1034)

Impact on Daily Living

On the FLIE questionnaire, significantly more patients taking the aprepitant regimen reported minimal or no impact on daily living overall (Fig 4). There 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%).

5-day period. There were no significant differences between the two treatment groups in reports of overall nausea (VAS < 5 mm; 33% for both) or significant nausea (VAS < 25 mm; aprepitant 61%, control 56%).

Ex. 1034, 2824, 2826-28

Aprepitant's Lack of Anti-Nausea Effects Led Field to Conclude That NK₁ Inhibitors May Not Impact Biological Nausea Pathways

Yeo 2008 (Ex. 1048)

[1]. 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, 534

Warr 2005 (Ex. 1034)

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. Patients frequently cite vomiting as a major concern of chemotherapy treatment, and hence, the aprepitant benefit has important clinical significance. There was no significant effect of aprepitant on nausea, though it is important to note again that the control group received active therapy with ondansetron for all 3 days, whereas the aprepitant group received ondansetron only on day 1. The more pronounced effect of aprepitant and 5-HT₃-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, 2828-29

Dr. Peroutka Confirmed That Warr (Ex. 1034) and Yeo (Ex. 1048) Reported No Statistically Significant Effects Against Nausea



Dr. Peroutka

Q. [A]t the end of the Warr reference, Exhibit 1034, looking at pages . . . 2828 to 2829, there's a paragraph that . . . says, "There." It continues: "Was *no significant effect of aprepitant on nausea.*" Do you see that?

A. Yes.

* * *

Q. That's what the authors wrote, correct?

A. Yes.

Ex. 2086, 211:14-212:12

* * *

Q. The P value for the nausea domain . . . Between the aprepitant-based regimen and the standard regimen without aprepitant [in Exhibit 1048 (Yeo)] is greater than 0.05, correct?

A. Yes.

Ex. 2086, 234:8-13

Azurity's Reply Turns to Numerical Superiority, Not Statistical Significance

Azurity's Reply

47-49), yet fails to show either claim requires this comparison. What the data does show is large percentages in both groups being successfully treated for nausea. POR 48, citing EX1030, Tables 1 & 2; EX1067, 125:9-131:19 (discussing the percentages of CINV patients with nausea successfully treated using the aprepitant triple therapy); EX1066 (Dr. Roeland's markings showing numbers of patients with no nausea or no significant nausea treated using standard therapy). As Helsinn concedes, "these tables show a *numerical* improvement in nausea parameters". POR 49 (original emphasis).

See, e.g., -945 Reply (Paper 26), 18-19

Herrington 2008 (Ex. 1016)

Other Efficacy Endpoints and Safety

The incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms (Table 4 and Fig. 2). In addition, the fre-

* * *

<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.¹⁶

Ex. 1016, 2084, 2086

"[N]umerical improvement" is insufficient to show a reasonable expectation of successfully achieving the *claimed* benefits in patients

See, e.g., -945 Sur-Reply (Paper 30), 13-14; see also -946 Sur-Reply (Paper 31), 15; -947 Sur-Reply (Paper 31), 15; -948 Sur-Reply (Paper 30), 15; -949 Sur-Reply (Paper 31), 16

Dr. Peroutka Confirmed That Herrington (Ex. 1016) Reported No Difference in the Treatment of Nausea



Dr. Peroutka

Q. [T]he authors of this [Herrington] article explicitly stated that: “The *incidence* of overall nausea, significant nausea (greater than 25 millimeter on the 100 millimeter visual analog scale), *and the severity of nausea was not different* among the three arms (Table 4 and Figure [2]).” Did I read that correctly?

A. That’s what they said. *And that’s how they interpreted it.*

Ex. 2086, 226:3-14

Azurity's Reply Pivot Is Untimely and Substantively Deficient

Azurity's Reply Pivot to Dexamethasone Is Untimely Reply Argument, and Should Be Disregarded

Azurity's Petition

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

Herrstedt teaches the triple therapy (with a NK₁ antagonist) is a more effective than without. EX1010, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin,’ was the primary end-point in all studies. Two of the HEC studies used an identical design comparing *ondansetron* * * * *aprepitant* days 2-3. In the Hesketh study, a complete response of 72.7% in the *aprepitant* arm versus 52.3% in the control arm was seen, and in the Poli-Bigelli study complete response rates were 62.7% versus 43.3%. The most recently published HEC study used the same design, except that *ondansetron* was included in the control arm for delayed protection days 2-4. Again a *statistical[] benefit favouring aprepitant was seen*, resulting in a complete response in the *aprepitant* arm of 72.0% versus 60.6% in the control arm.”) (parentheticals omitted). A POSA

-945 Petition (Paper 2), 42

Azurity's Reply

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 NK₁-inhibitor enhancement. *Netupitant*, an NK₁-inhibitor, would be expected to do this.

-945 Reply (Paper 26), 3

Azurity's Dexamethasone "Restoration" Argument Does Not Support a Reasonable Expectation of Success

Azurity's Reply

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 NK₁-inhibitor-*doubled* effectiveness: of course, the comparator will be ineffective by definition; however, using an NK₁-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 NK₁-inhibitor enhancement. Netupitant, an NK₁-inhibitor, would be expected to do this.

-945 Reply (Paper 26), 3

- Aprepitant failed to "restor[e]" half-dose of dexamethasone's "effectiveness against nausea," and Azurity has adduced no evidence that a POSA would expect otherwise with netupitant

"Half-dose" of dexamethasone (also recited in claims)

Herrington 2008 (Ex. 1016)

After informed consent was obtained, the patients were randomized to receive 1 of 3 regimens. 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 matching placebo on Days 2 and 3. Arm C involved palonosetron 0.25 mg intravenously and dexamethasone 18 mg orally on Day 1. The dexamethasone and aprepitant were

* * *

Other Efficacy Endpoints and Safety

The incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms (Table 4 and Fig. 2). In addition, the fre-

Ex. 1016, 2081, 2084

Reasonable Expectation of Successfully “treat[ing] nausea” Not Proven Where Addition of an NK₁ Inhibitor Can *Cause* Nausea



Dr. Peroutka

Q. [I]sn't it true that higher amounts *of aprepitant are known to have side effects of nausea?*

A. It can, yes.

Ex. 2086, 155:9-13

* * *

Q. [H]igher amounts of aprepitant have been known by 2009, according to you, to cause nausea. Isn't that true?

A. I said it's possible.

Ex. 2086, 156:10-17



Dr. Roeland

“Neither Herrstedt nor its cited studies support the broad premise that the addition of any NK-1 receptor antagonist will always improve the efficacy of a 5-HT₃ receptor antagonist and dexamethasone combination in the treatment of both nausea and vomiting. (Ex. 1010 at 146-47.) In fact, Dr. Peroutka admitted “*NK-1 receptor antagonists*” *could* “possibly” *result in “an adverse event of nausea,”* which could be extremely dangerous in already-vulnerable patients with cancer. (Ex. 2086 at 275:9-14.)”

Ex. 2088 (-945), ¶ 201

Azurity has failed to show that a POSA would have reasonably expected to successfully achieve, at least:

- 1 Claimed superiority of netupitant-based therapy ('826 patent)
- 2 Claimed treatment of nausea provided by netupitant, alone ('297 and '515 patents)
- 3 Claimed treatment of nausea provided by the combination of netupitant and palonosetron ('357 patent)

The '297 Patent Requires Claimed Nausea Benefits to Be Conferred by Administration of Netupitant

Claim 3 and Its Dependents

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

* * *

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.

Ex. 1004, 21:56-61, 23:1-3

Claim 1 and Its Dependents

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.

* * *

12. The method of claim 1, wherein said blood levels of netupitant are independently effective to prevent acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy.

Ex. 1004, 21:45-49, 22:22-25

Azurity's Petitions Failed to Provide Evidence Supporting a Reasonable Expectation of Successfully Practicing the *Claimed* Methods

Azurity's Petition

C. Claim 3: the prior art taught preventing nausea

1. 3[preamble]: “A method of preventing nausea during the acute and delayed phases of chemotherapy induced nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising”

To the extent the preamble is limiting, Herrstedt teaches it. Herrstedt teaches

* * *

Herrstedt teaches preventing nausea during the acute and delayed phases of chemotherapy, explaining its triple combination antiemetic improves efficacy “against acute emesis induced by highly or moderately emetogenic chemotherapy” and “is also active in the protection against delayed emesis.” EX1010, Abstract. A

-949 Petition (Paper 2), 27

Azurity's Petition

A. Claim 1 is an obvious modification of the prior art

1. [preamble]: “A method of preventing acute and delayed nausea and vomiting in a subject receiving highly emetogenic cancer chemotherapy comprising”

To the extent the preamble is limiting, Herrstedt teaches it. Herrstedt teaches

* * *

Herrstedt teaches its antiemetic combination effectively treats nausea and vomiting during the acute and delayed phases of emesis because its NK₁ antagonist “increases the effect of a serotonin₃-receptor antagonist plus a corticosteroid against acute emesis induced by highly or moderately emetogenic chemotherapy” and “is also active in the protection against delayed emesis.” EX1010, Abstract, 146 (“Complete response, defined as ‘no emesis and no rescue therapy on days 1-5 postcisplatin’, was the primary end-point in all studies.”), 148-149 & Table 4;

-949 Petition (Paper 2), 19

In addition to failing to justify its reliance on aprepitant data, Azurity's argument fails because “emesis” is distinct from nausea, and “complete response” does not correspond to the treatment of nausea

Azurity's Reply Pivot to Dexamethasone Fails to Support a Reasonable Expectation of Success

Azurity's Reply

2. For claim 3, preventing nausea in some subjects suffices

Claim 3 recites “preventing nausea” (EX1002, 21:56), which means no nausea in at least some patients (cf. EX1002, 18:10-15, defining “total control”), something even the prior art accomplished. EX1002, 19:Table 6 (showing “No Nausea” and “Total Control” in more than half the non-netupitant patients for both acute and delayed nausea); POR 10 (showing no nausea for more than half the *to standard therapy*). No such requirement appears in the contested claims. Hence, any treatment of nausea suffices, yet even Helsinn concedes that dexamethasone (one of the triple therapy components) treats nausea. EX1067, 117:23-118:2,

* * *

in claim 3 is met by any treatment that is more effective than placebo. The inclusion of an effective amount of dexamethasone (when used in combination with the NK₁-inhibitor) or palonosetron suffices.

-949 Reply (Paper 26), 3-4

Aprepitant's Failure to Treat Nausea Would Have Led a POSA to Reasonably Expect Failure with Netupitant, Not Success

Yeo 2008 (Ex. 1048)

[1]. 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, 534

Warr 2005 (Ex. 1034)

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. Patients frequently cite vomiting as a major concern of chemotherapy treatment, and hence, the aprepitant benefit has important clinical significance. There was no significant effect of aprepitant on nausea, though it is important to note again that the control group received active therapy with ondansetron for all 3 days, whereas the aprepitant group received ondansetron only on day 1. The more pronounced effect of aprepitant and 5-HT₃-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, 2828-29

**These Same Substantive Failures Likewise Defeat
Azurity's Obviousness Arguments Against the '515 Patent**

The '515 Patent Claims Recite Treating Nausea and Vomiting through Administration of a “single dose of netupitant”

'515 Patent Claims

1. A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising 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, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration, wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof if effective to treat said nausea and vomiting for said five consecutive days.

Ex. 1004, 22:2-19

'515 Patent Claims

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.

* * *

19. The method of claim 11, wherein said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.

Ex. 1004, 23:1-13, 24:15-18

Azurity's Petition Failed to Meaningfully Allege—Let Alone Prove—that a POSA Would Have Reasonably Expected a Single Dose of Netupitant to Treat Nausea

Azurity's Petition

H. Claim 19: “The method of claim 11, wherein said emesis inducing event is highly emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases.”

Building on the obviousness of claim 11, Herrstedt teaches treating CINV from HEC. EX1010, 146 (“cisplatin-based, highly emetogenic chemotherapy”). Herrstedt specifically teaches the NK₁ antagonist is “also active in the protection against delayed emesis.” *Id.*, Abstract, 146; EX1009, ¶¶563-65.

A POSA would have understood Herrstedt to teach an antiemetic therapy effective to achieve a “complete response”, i.e., to prevent or reduce the severity of nausea during the acute and delayed phases. EX1010, 146 (“Complete response,

* * *
hours after chemotherapy. *Id.*, 143. Hence, a POSA would have expected Herrstedt’s combination with netupitant as the NK₁ antagonist to treat both acute and delayed emesis. EX1009, ¶¶566-68.

-948 Petition (Paper 2), 26-27



Dr. Peroutka

Q. You will agree with me that *nausea is different than vomiting*, correct?

A. Correct.

Ex. 2086, 38:22-24



Dr. Roeland

The ‘complete response’ endpoint, however, *does not include nausea as a stated parameter*. Instead, a complete response only measures the ability to control vomiting.”

Ex. 2090 (-948), ¶ 53

Even Had Azurity Justified Relying on Aprepitant, It Would Not Have Supported an Expectation of Successfully Treating Nausea with a Single Dose of Netupitant

Yeo 2008 (Ex. 1048)

[1]. 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, 534

Warr 2005 (Ex. 1034)

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. Patients frequently cite vomiting as a major concern of chemotherapy treatment, and hence, the aprepitant benefit has important clinical significance. There was no significant effect of aprepitant on nausea, though it is important to note again that the control group received active therapy with ondansetron for all 3 days, whereas the aprepitant group received ondansetron only on day 1. The more pronounced effect of aprepitant and 5-HT₃-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, 2828-29

Azurity's Untimely Reply Argument Fails to Rehabilitate the Petition or Support a Reasonable Expectation of Successfully Achieving the Claimed Inventions

Azurity's Reply

Record evidence confirms that combining 5-HT₃- and NK₁-receptor antagonists improves the composite endpoints of complete protection and reduced rescue medication. Pet. 57-58, 62; EX1009, ¶¶1333-40, 1373. As Dr. Roeland

therapy. No such requirement appears in the contested claims. Hence, any treatment of nausea suffices, yet even Helsinn concedes that dexamethasone (one of the triple therapy components) treats nausea. EX1067, 117:23-118:2, 119:15-20; is met by any treatment that is more effective than placebo. The inclusion of an effective amount of dexamethasone (when used in combination with the NK₁-inhibitor) or palonosetron suffices.

-948 Reply (Paper 26), 2-3

- Fails to rebut Dr. Roeland's explanation that "complete protection" composite endpoint does not reflect treatment of nausea, alone
- Irrelevant to claims' requirement that a "single dose of netupitant" treats nausea

Azurity has failed to show that a POSA would have reasonably expected to successfully achieve, at least:

- 1 Claimed superiority of netupitant-based therapy ('826 patent)
- 2 Claimed treatment of nausea provided by netupitant, alone ('297 and '515 patents)
- 3 Claimed treatment of nausea provided by the combination of netupitant and palonosetron ('357 patent)

The '357 Patent Requires Treatment of Nausea Through Administration of Netupitant and Palonosetron (Not 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.

* * *

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.

* * *

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.

Ex. 1002, 21:48-51, 26:21-29, 45-48

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.

* * *

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.

Ex. 1002, 21:48-51, 26:21-29, 45-48

Azurity's Petition and Reply Arguments Fail for the Same Reasons Applicable to the Other Patent Family Members

Azurity's Petition Invokes Emesis, not Nausea

H. Claims 58-59: "The method of claim 54, wherein said chemotherapy is [highly/moderately] emetogenic chemotherapy, and said regimen is effective to prevent or reduce the severity of nausea during the acute and delayed phases."

* * *

Herrstedt describes efficacy of the drug combination on "emesis induced by highly or moderately emetogenic chemotherapy." EX1010, Abstract; *see id.*, 146,

Table 1, Table 4. Bös also teaches netupitant works well when administered before

* * *

Herrstedt discloses its antiemetic regimen is effective to treat "acute emesis induced by *highly or moderately emetogenic* chemotherapy," and is "also active in the protection against delayed emesis." EX1010, Abstract; EX1009, ¶¶972-73,

-946 Petition (Paper 2), 36-37

Azurity's Reply Turns to Dexamethasone

2. For claims 58 and 59, reducing nausea versus placebo suffices

Even for claims 58 and 59, the limitation "prevent or reduce the severity of nausea" (EX1002, 26:45-52) uses a disjunctive "or" making reduced nausea severity sufficient for obviousness. Although Helsinn suggests its claimed triple:

* * *

therapy. No such requirement appears in the contested claims. Hence, any treatment of nausea suffices, yet even Helsinn concedes that dexamethasone (one of the triple therapy components) treats nausea. EX2089, ¶59 ("significantly

* * *

recently emerged as a highly efficacious anti-nauseant", citing prior art). Thus, absent an express baseline, the nausea reduction in claims 58 and 59 is met by any treatment that is more effective than placebo. The inclusion of an effective amount of dexamethasone (when used in combination with the NK₁-inhibitor) is sufficient.

-948 Reply (Paper 26), 3-4

Agenda

- Serial motivation failures defeat every ground
- Failure to show a reasonable expectation of success
- Objective indicia confirm nonobviousness
- Failure to show that the prior art discloses every claim limitation

Skepticism of Claimed Patient Treatment Benefits Reflects Nonobviousness and Is Incompatible with a Reasonable Expectation of Success



WBIP, LLC, Plaintiff-Cross-Appellant,

v.

KOHLER CO., Defendant-Appellant.

United States Court of Appeals,
Federal Circuit.

Decided: July 19, 2016

[25, 26] Evidence of industry skepticism weighs in favor of non-obviousness. If industry participants or skilled artisans are skeptical about whether or how a problem could be solved or the workability of the claimed solution, it favors non-obviousness. Doubt or disbelief by skilled artisans regarding the likely success of a combination or solution weighs against the notion that one would combine elements in references to achieve the claimed invention. *See, e.g., Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 726 (Fed. Cir. 1990) (“[The infringer’s] skepticism is relevant and persuasive evidence of the nonobviousness of [the] invention.”); *Envtl. De-*

829 F.3d 1317, 1335 (Fed. Cir. 2016)

Prior Art Reflects That a POSA Would Have Been Skeptical of Using an NK1 Receptor Antagonist, Like Netupitant, to Treat Nausea

Yeo 2008 (Ex. 1048)

[1]. 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, 534

Warr 2005 (Ex. 1034)

aprepitant benefit has important clinical significance. There was no significant effect of aprepitant on nausea, though it is important to note again that the control group received active therapy with ondansetron for all 3 days, whereas the aprepitant group received ondansetron only on day 1. The more pronounced effect of aprepitant and 5-HT₃-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, 2828-29

Schmoll 2006 (Ex. 2073)

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 [11] or moderately [18] emetogenic chemotherapy, which suggests that the neurokinin-1 receptor antagonists may have less impact on the nausea component of chemotherapy-induced nausea and vomiting. In general, the control of nausea lags

Ex. 2073, 1005



Dr. Roeland

“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.*”

Ex. 2088 (-945), ¶ 263; Ex. 2089 (-946, -947), ¶ 250; Ex. 2090 (-948), ¶ 247; Ex. 2091 (-949), ¶ 245

Helsinn Showed and Claimed That Netupitant-Based Triple Therapy—Unlike Aprepitant—Provides a Statistically Significant Improvement in Nausea Treatment in Cancer Patients

'826 Patent Specification

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

Regimen of
palonosetron and
dexamethasone

'826 Patent, 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 (NK₁) 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.

Ex. 2088 (-945), ¶ 256; Ex. 2089 (-946, -947), ¶ 243; Ex. 2090 (-948), ¶ 240; Ex. 2091 (-949), ¶ 238

Ex. 1001, 21:39-63

See, e.g., -945 POR (Paper 22), 65-66, Section VII.A; -945 Sur-Reply (Paper 30), 22-24; -946 POR (Paper 23), 55-56; -946 Sur-Reply (Paper 31), 21-24; -947 POR (Paper 23), 57-58; -947 Sur-Reply (Paper 31), 21-23; -948 POR (Paper 22), 60-61; -948 Sur-Reply (Paper 30), 22-24; -949 POR (Paper 23), 56-57; -949 Sur-Reply (Paper 31), 22-24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

91

Unexpected Nausea Treatment Disclosed and Claimed Further Reflects Nonobviousness

The PROCTER & GAMBLE
COMPANY, Plaintiff-
Appellee,

v.

TEVA PHARMACEUTICALS USA,
INC., Defendant-Appellant,
United States Court of Appeals,
Federal Circuit.

May 13, 2009.

The district court found that, even if Teva could establish a prima facie case of obviousness, P & G had introduced sufficient evidence of unexpected results to rebut such a showing. Such evidence included “test data showing that the claimed composition[] possess[es] unexpectedly improved properties or properties that the prior art does not have.” *In re Dillon*, 919 F.2d 688, 692–93 (Fed.Cir.1990). Because Teva did not establish a prima facie case of obviousness, P & G need not rely on this evidence to defend the '122 patent.

* * *

Dr. Miller stated that the superior properties of risedronate were unexpected and could not have been predicted. In a

566 F.3d 989, 997 (Fed. Cir. 2009)

'826 Patent Specification

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. 2088 (-945), ¶ 260; Ex. 2089 (-946, -947), ¶ 247;
Ex. 2090 (-948), ¶ 244; Ex. 2091 (-949), ¶ 242

Even Applying the Analysis That Azurity Prescribes, Netupitant's Unexpected Anti-Nausea Benefits Confirm Its Failure to Prove Obviousness

Azurity's Reply: "Unexpected results must be based on comparison with the closest prior art and must represent a *difference in kind* rather than a difference in degree."

-945 Reply (Paper 26), 22

"Closest Prior Art": Aprepitant Triple Therapy

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 matching placebo on Days 2 and 3. Arm C involved palonosetron 0.25 mg intravenously and dexamethasone 18 mg orally on Day 1. The dexamethasone and aprepitant were encapsulated to maintain blinding among the 3 arms. On Days 1–3, placebo resembling aprepitant was administered. All patients in the 3 study arms

Ex. 1016, 2081

Results of Aprepitant Triple Therapy: No Nausea Impact

Other Efficacy Endpoints and Safety

The incidence of overall nausea, significant nausea (>25 mm on the 100-mm visual analog scale), and the severity of nausea was not different among the 3 arms (Table 4 and Fig. 2). In addition, the frequency of rescue antiemetics was also similar among the 3 groups (Table 5). During the first 24

Ex. 1016, 2084

Relevant "difference in kind": Aprepitant-based therapy failed to provide benefits in nausea, while netupitant-based therapy yielded statistically significant nausea improvements in human patients

Unexpected Synergy Between Netupitant and Palonosetron Provides Further Evidence of Nonobviousness

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	
No Drug (Default)	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	
No Impact on Substance P Inhibition		Plus net (30 nM) plus palo (6 nM)	970 ± 150 ^c	5

Sixty-Fold Increase in Substance P Inhibition

Ex. 2088 (-945), ¶ 266; Ex. 2089 (-946, -947), ¶ 253; Ex. 2091 (-949), ¶ 248

'826 Patent Specification

In another embodiment, the netupitant is combined with other anti-emetic agents, including a 5-HT₃ antagonist such as palonosetron and a corticosteroid such as dexamethasone, in a manner that results in even greater efficacy against nausea. It has been discovered that palonosetron is much more effective in combinations with netupitant than it is in combination with aprepitant, as reported by Grunberg et al., Support Cancer Care (2009) 17:589-594. In addition, palonosetron

Ex. 1001, 4:65-5:5



Dr. Roeland

“[W]hen the inventors combined netupitant and palonosetron, *even at concentrations where neither compound alone* increased the EC₅₀ of substance P, the combination increased the EC₅₀ of substance P from μM to 120 μM. This value was a **60-fold increase** in the EC₅₀ of substance P, whereas the additive increase should have been zero.

Ex. 2088 (-945), ¶ 268; Ex. 2089 (-946, -947), ¶ 255; Ex. 2091 (-949), ¶ 250

See, e.g., -945 POR (Paper 22), 8-12; -945 Sur-Reply (Paper 30), 24; -946 POR (Paper 23), 9-12; -946 Sur-Reply (Paper 31), 23-24; -947 POR (Paper 23), 9-12; -947 Sur-Reply (Paper 31), 23; -948 Sur-Reply (Paper 30), 23-24; -949 POR (Paper 23), 9-12; -949 Sur-Reply (Paper 31), 24

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Azurity Fails to Rebut the Inventors' Evidence-Supported Conclusion of Synergy

Azurity's Reply: "Helsinn argues that its inventors *hypothesized* a synergy between netupitant and palonosetron. Inventor speculation is not proof. Helsinn fails to address, much less rebut, the petition's showing that any purported synergy . . . arises from using palonosetron with any NK₁-inhibitor, not from netupitant alone."

-945 Reply (Paper 26), 23 (citations omitted)

Thomas 2014 (Ex. 1045)

Recent studies using NG108-15 cells known to express both the 5-HT₃ and NK₁ receptors (Reiser and Hamprecht 1989; Emerit et al. 1993) showed that netupitant and palonosetron exhibit a synergistic effect in the prevention of the NK₁ receptor response against its endogenous agonist substance P (Stathis et al. 2012). The results suggest that palonosetron's effect is distinct in the presence of an NK₁ 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 NK₁ receptor internalization and that when used in combination their effect becomes additive. NK₁ receptor inter-

receptors (Rojas et al. 2014). These molecular interactions may be responsible for palonosetron's clinical profile. It is not clear however, if palonosetron's suppression of delayed emesis would be synergistic, additive or obscured when used in combination with NK₁ receptor antagonists.

Ex. 1045, 2638

Agenda

- Serial motivation failures defeat every ground
- Failure to show a reasonable expectation of success
- Objective indicia confirm nonobviousness
- Failure to show that the prior art discloses every claim limitation

As the Patent Challenger, Azurity Bore the Burden to Show That the Prior Art Disclosed “all claimed limitations”



PAR PHARMACEUTICAL, INC., and
Alkermes Pharma Ireland Limited,
Plaintiffs–Appellants,

v.

TWI PHARMACEUTICALS, INC.,
Defendant–Appellee.

United States Court of Appeals,
Federal Circuit.

Dec. 3, 2014.

We first must determine whether TWi carried its burden to prove that all claimed limitations are disclosed in the prior art. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1164 (Fed.Cir.2006) (stating that we consider motivation to combine and reasonable expectation of success only “if all the elements of an invention are found in a combination of prior art references”).

773 F.3d 1186, 1194 (Fed. Cir. 2014)

“Striatum-Occupancy” Claim Limitation Present in Each Patent

'826 Patent

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 (NK₁) 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.

Ex. 1001, 21:39-63

'357 Patent

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.

- * * *
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.

- * * *
24. The method of claim 19, wherein said netupitant occupies at least 70% of said patient's striatum NK1 receptors ninety-six hours after said administration.

Ex. 1002, 21:35-38, 22:62-23:10, 23:60-62

“Striatum-Occupancy” Claim Limitation Present in Each Patent

'515 Patent

1. A method of treating nausea and vomiting from an emesis-inducing event for a period of five consecutive days in a patient in need thereof, comprising 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, and which enters the systemic circulation, crosses the blood brain barrier and occupies 70% or more of NK₁ receptors in the striatum seventy-two hours after said administration, wherein a single dose of netupitant or pharmaceutically acceptable salt thereof is administered on day one of said five consecutive days, no further netupitant or pharmaceutically acceptable salt thereof is administered during said five consecutive days, and said single dose of netupitant or pharmaceutically acceptable salt thereof is effective to treat said nausea and vomiting for said five consecutive days.

Ex. 1003, 22:2-19

'297 Patent

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.

* * *

7. The method of claim 1, wherein said netupitant occupies at least 70% of said patient's striatum NK₁ receptors seventy-two hours after said administration.

Ex. 1004, 21:45-49, 22:10-12

Common Specification Identifies the Duration of NK₁ Receptor Occupancy Provided by Netupitant as an Advantage of the Claimed Methods

'826 Patent

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK₁ receptors in the brain. In particular, it has been discovered that netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK₁ receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

Ex. 1001, 4:37-51

'826 Patent

TABLE 6

SUMMARY OF SECONDARY EFFICACY RESULTS: PERCENT OF PATIENTS, MFAS POPULATION						
Efficacy endpoint	Palo alone (n = 136)	Palo + Netu 100 mg (n = 135)	Palo + Netu 200 mg (n = 137)	Palo + Netu 300 mg (n = 135)	Aprepitant Regimen (N = 134)	Palo + Aprep 285 mg (N = 41)**
No 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. 2088 (-945), ¶ 260

Patent Discloses that Striatum Receptor Occupancy Impacted by Dose of Netupitant Administered to Patient

'826 Patent

Example 4

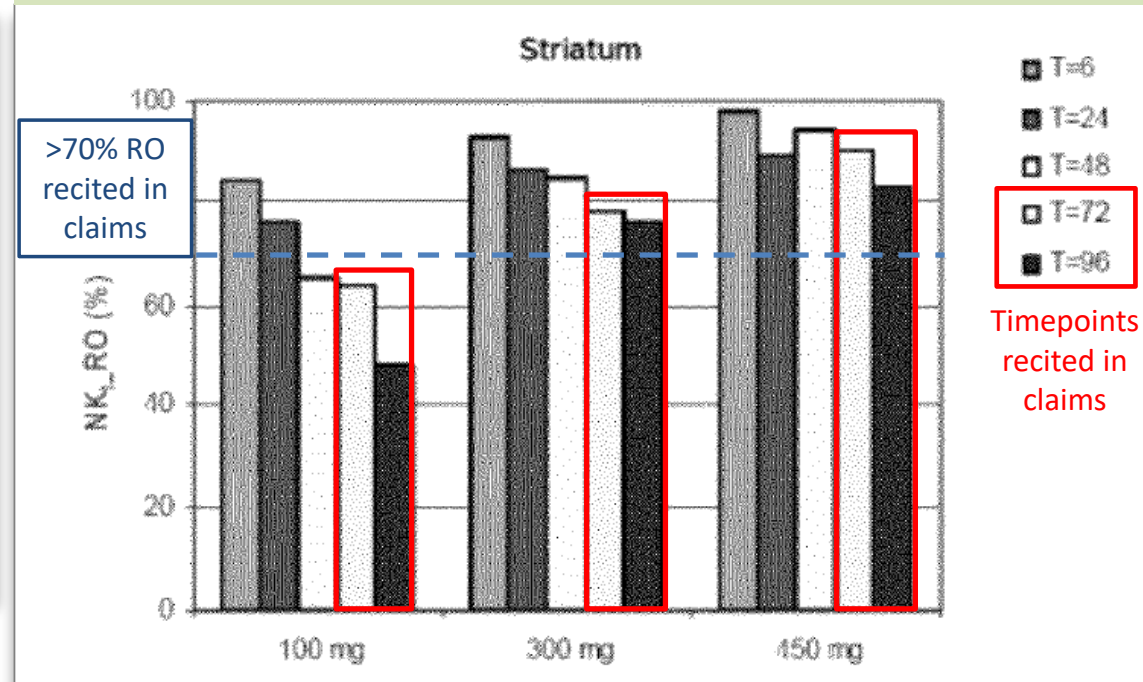
Netupitant Pet Receptor Occupancy Study

* * *

All doses showed a relatively long duration of blockade of NK₁ receptors and the decline over time was dose dependent. In the 100 mg. dose group, 4 of 6 regions still had a mean NK₁-RO over 70% at 96 hours post dose. In the highest dose group (450 mg), 5 of 6 regions had a mean NK₁-RO of 80% or higher at 96 hours post dose. A comparison of the results for the dose groups (100 mg., 300 mg. and 450 mg) showed a consistent but small increase in NK₁-ROs with increasing netupitant dose. (FIG. 5)

Ex. 1001, Example 4 (16:36-60)

'826 Patent



Ex. 1001, Figure 5

Azurity Proves Neither of Its Two, Distinct Receptor Occupancy Limitation Arguments

'826 Patent, Claim 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 (NK1) receptors in the striatum seventy-two hours after said administration . . .*

1. Receptor Occupancy Not a Limitation (Construction)

Moreover, nothing in Helsinn's argument overcomes the grammatical significance of Helsinn's choice of "which" to start the clause, making clause descriptive rather than limiting. Pet. 9-10; cf. *Minton v. National Association of Securities Dealers*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ("A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited."). Nor does Helsinn rebut Hargreaves use of

See, e.g., -945 Reply (Paper 26), 7-8

2. Receptor Occupancy Inherent (Substantive)

For claim element 1(a)[2], "a therapeutically effective amount *which*" means the functions following "which" describe inherent properties rather than therapeutic effects that might further restrict a therapeutically-effective amount. *In*

See, e.g., -945 Petition (Paper 2), 9-10

Claim Construction: Azurity's Attempt to Read out the Striatum Receptor Occupancy Limitation Fail

Minton Does Not Support Construing the Receptor Occupancy Limitation as Descriptive and Non-Limiting

Azurity's Reply: "Claim 1's striatum-occupancy element is *descriptive* Helsinn's choice of 'which' to start the clause, making clause [sic] descriptive rather than limiting. Pet. 9-10; cf. *Minton v. National Association of Securities Dealers*, 336 F.3d 1373, 1381 (Fed. Cir. 2003) ('A whereby clause in a method claim in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.')."

-945 Reply (Paper 26), 6-8



Vernon F. MINTON, Plaintiff-Appellant,

v.

NATIONAL ASSOCIATION OF SECURITIES DEALERS, INC. and The Nasdaq Stock Market, Inc., Defendants-Appellees.

United States Court of Appeals,
Federal Circuit.

July 29, 2003.

1. A method for trading securities between individuals, comprising:

* * *

executing a trade of the security based on information contained in the offer for consideration specified in the reply to the offer, whereby the security is traded efficiently between the first [offering] individual and the second [replying] individual;

* * *

336 F.3d 1373, 1380-81 (Fed. Cir. 2003)

[9] The district court was also correct in not giving weight to the "traded efficiently" phrase in the whereby clause of the executing step. A whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited. *Tex. Instruments Inc. v. U.S. Int'l Trade Comm'n*, 988 F.2d 1165, 1172 (Fed.Cir. 1993). That is the case here. The term "efficiently" on its face does not inform the mechanics of how the trade is executed, and nothing in the specification or the prosecution history suggests otherwise. Rather, the term "efficiently" is a laudatory one characterizing the result of the executing step. We therefore hold that

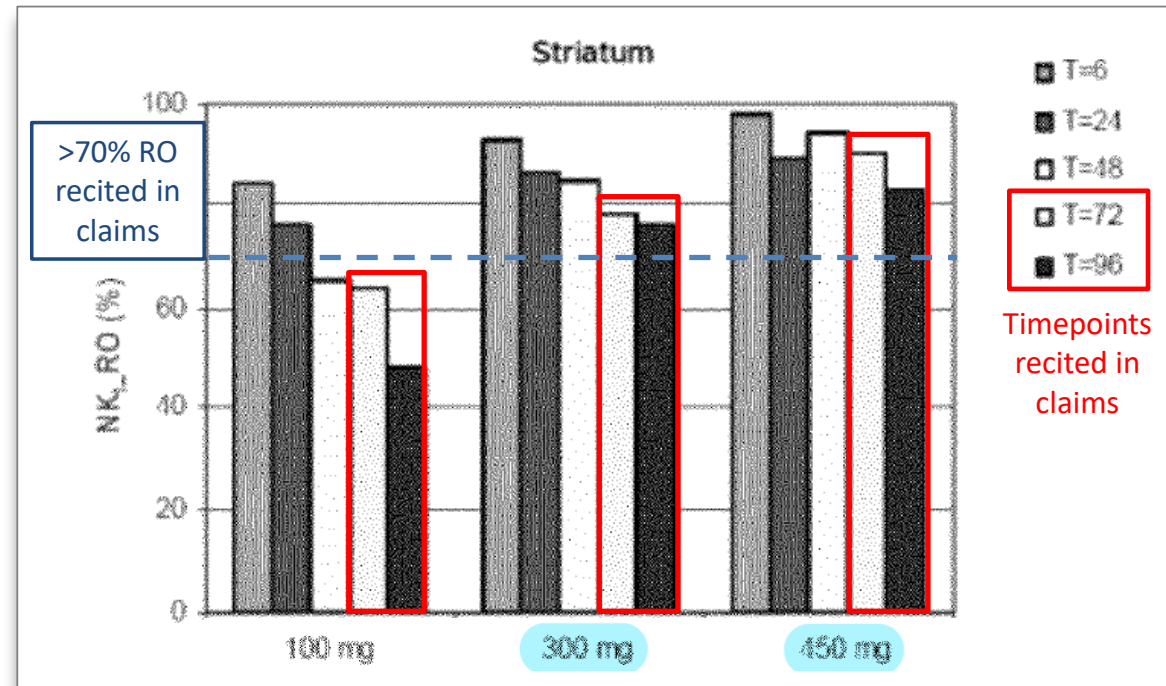
Striatum Receptor Occupancy Limitation Dictates How the Claimed Methods of Treatment Are Carried Out

Minton, 336 F.3d at 1381: “The term ‘efficiently’ on its face *does not inform the mechanics of how the trade is executed* and nothing in the specification or the prosecution history suggests otherwise. Rather, the term ‘efficiently’ is a laudatory one characterizing the result of the executing step.”

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 (NK₁) receptors in the striatum seventy-two hours after said administration;

Ex. 1001, 21:39-63

“[I]nform[s] the mechanics of how” the treatment method is carried out by dictating how much netupitant is administered



Ex. 1001, Figure 5

Minton Is Inapposite Where Intrinsic Record Reflects That “wherein/whereby” Clause Is Part of the Claimed Method

Hoffer v. Microsoft Corp., 405 F.3d 1326 (Fed. Cir. 2005): “21. A *method of messaging* among at least two remote user terminals . . . *whereby* a trade network supports users at said plurality of RUTs who are each guided by said IAPI to select an economic activity, to identify that index topic that corresponds to said activity, to enter that topic board dedicated to said topic, and who are collectively able to concurrently engage in interactive data messaging on said topic boards.”

The “Whereby” Clause

[7] Mr. Hoffer states that the district court erred in holding that the “whereby” clause limits the claims, pointing out that the Federal Circuit has held that “a whereby clause in a method claim is not given weight when it simply expresses the intended result of a process step positively recited.” *Minton v. Nat’l Ass’n of Securities Dealers, Inc.*, 336 F.3d 1373, 1381 (Fed.Cir.2003). It is correct that a “whereby” clause generally states the result of the patented process. However, when the “whereby” clause states a condition that is material to patentability, it cannot be ignored in order to change the substance of the invention.

The whereby clause describes a network of users at multiple remote user terminals who are “collectively able to concurrently engage in interactive data messaging.” This capability is more than the intended result of a process step; it is part of the process itself. This interactive element is described in the specification and prosecution history as an integral part of the invention. The “Summary of the Inven-

405 F.3d 1326, 1329-30 (Fed. Cir. 2005)

Federal Circuit Precedent Confirms *Minton* Is Inapplicable Here

Allergan Sales, LLC v. Sandoz, Inc., 935 F.3d 1370 (Fed. Cir. 2019): “1. A *method of treating a patient with glaucoma* . . . comprising topically administering twice daily to an affected eye a single composition comprising 0.2% w/v brimonidine tartrate and 0.68% w/v timolol maleate, *wherein* the method is as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day and *wherein* the method reduces the incidence of one o[r] more adverse events”

The specification of the Patents-in-Suit demonstrates that the claimed invention is ultimately a formulation (and methods of using that formulation) that allows for increased efficacy and safety, i.e., a decreased risk of adverse events. See '453

* * *
ed”). The prosecution history thus demonstrates that the formulation’s efficacy and safety—as reflected in the disputed “wherein” clauses—were expressly relied on to define the claimed methods and distinguish them from the prior art.

935 F.3d at 1375-76;
id. at 1379 (Prost, CJ., concurring)

Nor does the text of claim 1 suggest that these specific benchmarks are “only a statement of purpose and intended result.” *Bristol-Myers Squibb*, 246 F.3d at 1376. On their face, these clauses state specific requirements rather than a general purpose or aspirational result for the claimed method. The efficacy clause does not simply require some general level of therapeutic effectiveness. Instead, it specifically requires that the claimed formulation be “as effective as the administration of 0.2% w/v brimonidine tartrate monotherapy three times per day.” '453 patent col. 9 l. 20–col. 10 l. 1.

* * *
In light of this claim language, Sandoz’s attempt to liken the clauses here to the non-limiting term in *Minton* founders. In

Applying Governing Precedent, the Intrinsic Record Shows That the Striatum Receptor Occupancy Limitation Is Limiting

Hoffer: “whereby clause . . . is described in the *specification* and prosecution history as an integral part of the invention”

SUMMARY OF THE INVENTION

After extensive testing into the clinical effects of netupitant, it has unexpectedly been discovered that netupitant is active against nausea, and that a single dose of netupitant is able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. It has also been discovered, quite unexpectedly, that netupitant exhibits unique binding habits to NK₁ receptors in the brain. In particular, it has been discovered that netupitant binds to NK₁ receptors in the striatum in a long-lasting manner, and that less than 20 or 30% of netupitant is released from striatum NK₁ receptors even ninety-six hours after administration. This is in stark contrast to aprepitant, in which receptor binding drops swiftly over time, and must be dosed repeatedly if emesis control is desired throughout the delayed phase; and which shows no meaningful effect against nausea.

Ex. 1001, 4:37-51

Allergan: “these clauses state *specific requirements* rather than a general purpose or aspirational result”

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 (NK₁) receptors in the striatum seventy-two hours after said administration;

Ex. 1001, 21:39-46

Azurity's Counter-Argument Is Incompatible with Federal Circuit Precedent and Ignores the Claims

Azurity's Reply: “Significantly, Helsinn did not point to any additional step in claim 1 beyond administration that would achieve the claimed effect.”

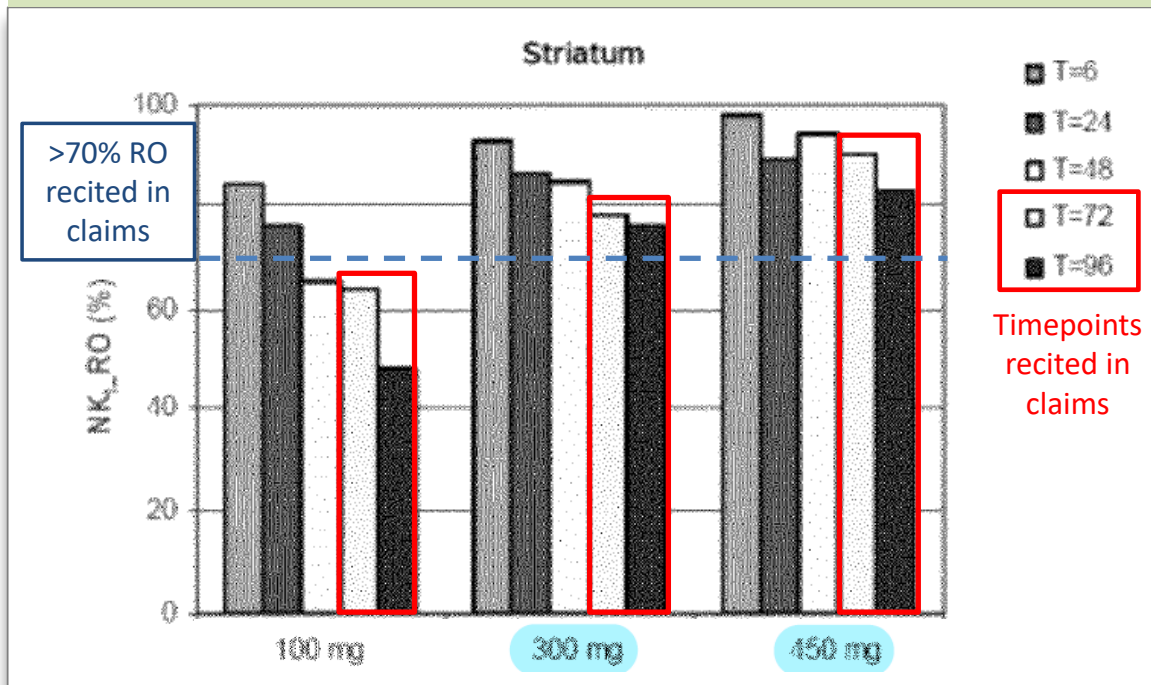
-945 Reply (Paper 26), 6

Allergan

Sandoz contends that these clauses “merely state ... intended results,” Appellant’s Br. 36, because they reflect the results of administering the Example I formulation, viz., Combigan®, as witnessed during the Example II clinical study, *see, e.g., id.* at 36 (“The asserted method claims have one and only one step: administration of the claimed composition. Everything else is literally the results observed during clinical trials of Combigan[®].”); *see also Minton*

* * *
generally not limiting). We disagree. While we recognize some overlap between the language of the “wherein” clauses and those results, we must read the claims in view of the “entire specification.” *Si-*

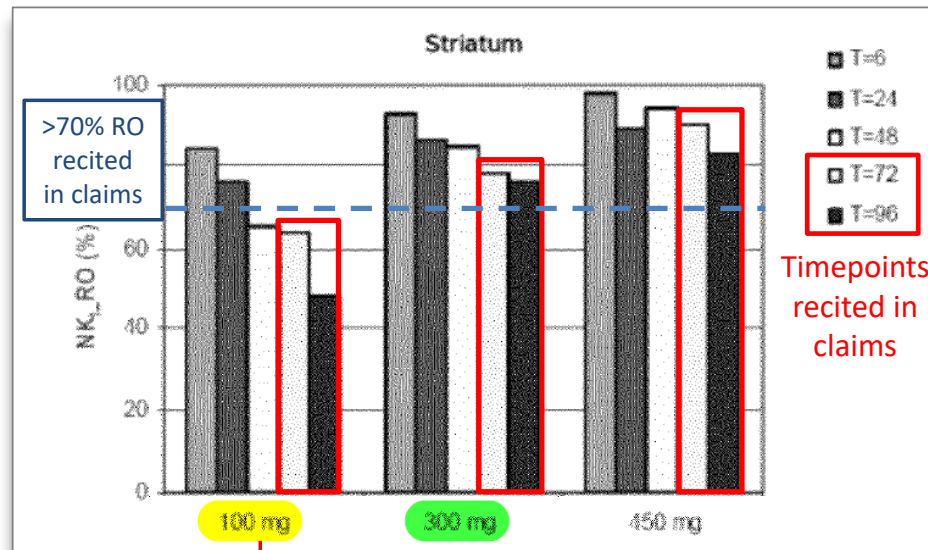
Striatum Receptor Occupancy Limitation Dictates *What* Is Administered (*i.e., Amount* of Netupitant)



See, e.g. -945 Sur-Reply (Paper 30), 16-18; -946 Sur-Reply (Paper 31), 16-17; -947 Sur-Reply (Paper 31), 16-17; -948 Sur-Reply (Paper 30), 16-18; -949 Sur-Reply (Paper 31), 17-18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 109

Amounts that Treat Vomiting Will Not Necessarily Occupy at least >70% NK₁ Receptors



Ex. 1001, Figure 5

100 mg provides statistically significant benefits in vomiting

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

Ex. 1001, Table 6

Azurity's Conclusory Assertions of Inherency Fall Well Short of Carrying Its Burden to Prove Unpatentability

Inherency Is a High Burden That Must Be Proven with Evidence, Not Argument



PERSONALWEB TECHNOLOGIES,
LLC, Appellant

v.

APPLE, INC., Appellee
United States Court of Appeals,
Federal Circuit.

Decided: March 8, 2019

enough. “Inherency . . . may not be established by probabilities or possibilities.” *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). “The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Id.* (emphasis added). Rather, a party must “show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function.” *Id.* (emphasis in original).

917 F.3d 1376, 1382 (Fed. Cir. 2019)



CYTIVA BIOPROCESS R&D
AB, Appellant

v.

JSR CORP., JSR Life Sciences,
LLC, Cross-Appellants

United States Court of Appeals,
Federal Circuit.

Decided: December 4, 2024

inherent property. Further, a petitioner must still meet its burden to demonstrate that the claimed limitation is indeed inherent. Simply saying it is so without sufficient evidence will not demonstrate unpatentability.

122 F.4th 876, 889 n.15

Azurity's Inherency Arguments Rely on Mere Probabilities Extrapolated—Without Support—from Insufficient Aprepitant Data

Azurity's Petition

Hargreaves teaches a therapeutically-effective amount occupies at least about 75% of striatum NK₁ receptors EX1012, Fig. 4(A); EX1009, ¶258.

-945 Petition (Paper 2), 35



Dr. Roeland's Unrebutted Testimony

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*) This data would not have disclosed to a POSA what aprepitant's NK-1 receptor occupancy was **72** hours after administration, much less what netupitant's NK-1 receptor occupancy was **72** hours after administration, as required by the claim.

Ex. 2088 (-945), ¶ 193

Azurity can point to *no* prior art disclosures or data regarding the striatum receptor occupancy of netupitant, and its aprepitant data is limited to *30 hours*, not *72 hours* as claimed

Dr. Peroutka's Deposition Concessions Confirm That Azurity Has Not Proven Its Conclusory Inherency Allegations



Dr. Peroutka

Q. Do you have any data whatsoever to determine the comparison of [receptor binding] affinity between aprepitant and netupitant in the prior art?

A. *It was out of scope. I didn't look it up.*

Ex. 2086, 242:25-243:5

* * *

Q. And you have not provided any data whatsoever comparing how casopitant, netupitant, or aprepitant, *how long they remain bound or interact with the NK-1 receptor*, correct?

A. Well, how long they're bound is a measure of affinity. Basically, the tighter you bind, the higher affinity, you're going to have, so. But *specifically, no. I did not find that in the scope.*

Q. You did not. So let's be clear. You did not *analyze the affinity* between casopitant, netupitant, and aprepitant for the NK-1 receptor, right?

A. *Correct.*

Ex. 2086, 254:2-17

Unable to Rehabilitate Hargreaves' Shortcomings, Azurity's Reply Argues Inherency Even More Broadly

Azurity's Reply

Helsinn argues that nothing connects Hargreaves to netupitant (POR59), but this misses the point. Hargreaves teaches a proxy for NK₁-inhibitor effectiveness. Because netupitant is an NK₁-inhibitor, an effective amount of netupitant **must** meet Hargreaves receptor-occupancy threshold. Rather than address this syllogism,

-945 Reply (Paper 26), 20

PersonalWeb Techs. LLC

enough. “Inherency . . . may not be established by probabilities or possibilities.” *PAR Pharm., Inc. v. TWI Pharm., Inc.*, 773 F.3d 1186, 1195 (Fed. Cir. 2014). “The mere fact that a certain thing *may* result from a given set of circumstances is not sufficient.” *Id.* (emphasis added). Rather, a party must “show that *the natural result flowing* from the operation as taught would result in the performance of the questioned function.” *Id.* (emphasis in original).

917 F.3d 1376, 1382 (Fed. Cir. 2019)

Azurity has not shown that *every* dose of an NK₁ inhibitor that treats nausea and vomiting *must* “occup[y] at least 70% of neurokinin-1 (NK₁) receptors in the striatum” 72 hours after administration

Patent Owner's Demonstratives

United States Patent and Trademark Office
Before the Patent Trial and Appeal Board

Azurity Pharmaceuticals, Inc., Petitioner v. Helsinn Healthcare S.A., Patent Owner

U.S. Patent Nos. 8,623,826, 9,186,357, 9,943,515, and 10,828,297

Cases: IPR2025-00945, -00946, -00947, -00948, and -00949

Oral Hearing: September 15, 2026