

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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AZURITY PHARMACEUTICALS, INC.,  
Petitioners,

v.

HELSINN HEALTHCARE S.A.,  
Patent Owner.

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IPR2025-00945  
Patent 8,623,826 B2

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Before MICHAEL J. FITZPATRICK, SHERIDAN K. SNEDDEN, and  
CHRISTOPHER J. PAULRAJ, *Administrative Patent Judges*.

SNEDDEN, *Administrative Patent Judge*.

DECISION  
Granting Institution of *Inter Partes* Review  
35 U.S.C. § 314

## I. INTRODUCTION

Petitioner, Azurity Pharmaceuticals, Inc., filed a Petition to institute an *inter partes* review of claim 1–25 of U.S. Patent No. 8,623,826 B2 (Ex. 1001, “the ’826 patent”). Paper 2 (“Pet.”). Patent Owner, Helsinn Healthcare S.A., filed a Preliminary Response. Paper 10 (“Prelim. Resp.”).

Patent Owner also filed a discretionary denial brief, and Petitioner filed an opposition thereto. Papers 7 and 8. On September 19, 2025, then Acting Director Stewart denied the request for discretionary denial and referred the Petition to the Board for a consideration on the merits. Paper 11, at 3–4.

We have the authority to determine whether to institute an *inter partes* review. 35 U.S.C. § 314; 37 C.F.R. §42.4(a). We may not institute an *inter partes* review “unless . . . there is a reasonable likelihood that the petitioner would prevail with respect to at least 1 of the claims challenged in the petition.” 35 U.S.C. § 314(a). Upon consideration of the Petition and the Preliminary Response, and for the reasons explained below, we determine that there is a reasonable likelihood that Petitioner would prevail with respect to at least one claim. Accordingly, we grant the Petition

## II. BACKGROUND

### A. *Real Parties in Interest*

Each party identifies itself as the sole real party in interest (RPI). Pet. 69; Paper 4, at 1. There is no dispute over RPIs in this proceeding.

### B. *Related Matters*

The parties identify the following concurrently-filed *inter partes* review proceedings as related matters: IPR2025-00946 (challenging claims

2–4, 11–16, 40–42, and 52–62 of Patent 9,186,357), IPR2025-00947 (challenging claims 1, 5–10, 17–39, and 43–51 of Patent 9,186,357), IPR2025-00948 (challenging claims 1–23 of Patent 9,943,515), and IPR2025-00949 (challenging claims 1–23 of Patent 10,828,297). Pet. 62; Paper 5, 1.

*C. The '826 patent (Ex. 1001)*

*i. Specification*

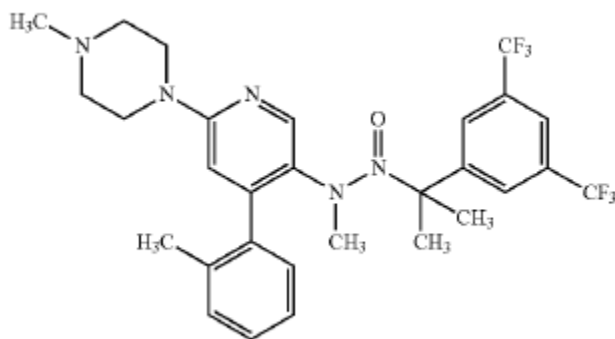
The '826 patent is titled “Compositions and Methods for Treating Centrally Mediated Nausea and Vomiting.” Ex. 1002, code (54). The '826 patent issued from Appl. No. 13/077,462, which claims priority back to Provisional Application No. 61/262,470 filed on November 18, 2009. *Id.* at codes (21), (22), (60), (63). There is no dispute over the priority date for the '826 patent.

The '826 patent relates to the use of centrally acting NK antagonists to treat chemotherapy-induced nausea and vomiting (CINV), and in particular treatment regimens using the combination of the 5-HT<sub>3</sub> antagonist palonosetron and the NK<sub>1</sub> antagonist netupitant. *Id.* at 1:19–25, 4:7–33. The patent also discusses the use of the corticosteroid dexamethasone as part of such a regimen. *Id.* at 1:32–36, 4:31–33.

As explained in the '826 patent, the prior art recognized the use of 5-HT<sub>3</sub> antagonists, such as ondansetron and palonosetron, to control nausea and vomiting caused by various medical procedures, including chemotherapy (CINV), surgery (PONV), and radiation therapy (RINV). *Id.* at 1:28–38. The background section of the patent further notes that NK<sub>1</sub> antagonists recently emerged as another tool for combating nausea and vomiting from emetogenic medical procedures. *Id.* at 2:4–6. The patent

indicates that the NK<sub>1</sub> antagonist aprepitant was approved by the Food and Drug Administration (FDA) and marketed as EMEND®, but notes that aprepitant did not show a reduction in nausea compared to other components of the anti-emetic regimen. *Id.* at 2:6–34. There was also a limited effect on nausea by another known NK<sub>1</sub> antagonist, casopitant. *Id.* at 2:34–49.

The '826 patent teaches that netupitant is another selective NK<sub>1</sub> antagonist under development by Patent Owner, with the formula 2-3,5-bis(trifluoromethyl)phenyl-N,2-dimethyl-N-4-(2-methylphenyl)-6-(4-methylpiperazin-1-yl)pyridin-3-ylpropanamide and the following structure:



*Id.* at 2:65–3:20. The figure above shows the chemical structure of netupitant. The patent explains that, after extensive clinical testing, it was unexpectedly discovered that netupitant is active against nausea, and that a single dose of netupitant was able to treat nausea and vomiting in response to highly and moderately emetogenic chemotherapy for five consecutive days. *Id.* at 4:37–42.

Additionally, the '826 patent teaches that netupitant may be combined with other anti-emetic agents, including a 5-HT<sub>3</sub> antagonist such as palonosetron and a corticosteroid such as dexamethasone, to achieve unexpectedly improved treatment outcomes. *Id.* at 4:65–67. For example, the patent explains that palonosetron is much more effective in combinations

with netupitant than it is in combination with aprepitant, and that palonosetron shows an improved pharmacokinetic profile (e.g., better bioavailability) when combined with netupitant as opposed to palonosetron administered in a single dose. *Id.* at 5:2–9. The patent further explains that netupitant potentiates the effect of dexamethasone, such that dexamethasone may be administered at “sub-therapeutic doses” (i.e., doses at which dexamethasone would be ineffective if administered by itself). *Id.* at 5:13–17. In support, the patent includes data on both a complete response rate (defined as no emetic episodes, no rescue medication) and various secondary endpoints (including no emesis, no nausea, and no significant nausea) from a clinical efficacy study comparing a) netupitant (at doses of 100 mg, 200 mg, and 300 mg) combined with 0.5 mg palonosetron and a sub-therapeutic dose of dexamethasone (12 mg on Day 1) to b) 0.5 mg palonosetron combined with a standard dexamethasone dose (20 mg on Day 1) and c) aprepitant regimens combined with either ondansetron or palonosetron and dexamethasone. *Id.* at 16:65–19:45; Tables 5 and 6.

Example 4 of the '826 patent discloses administering netupitant alone to healthy human volunteers to determine occupancy of brain NK<sub>1</sub> receptors. The results are shown in Figure 5, reproduced below:

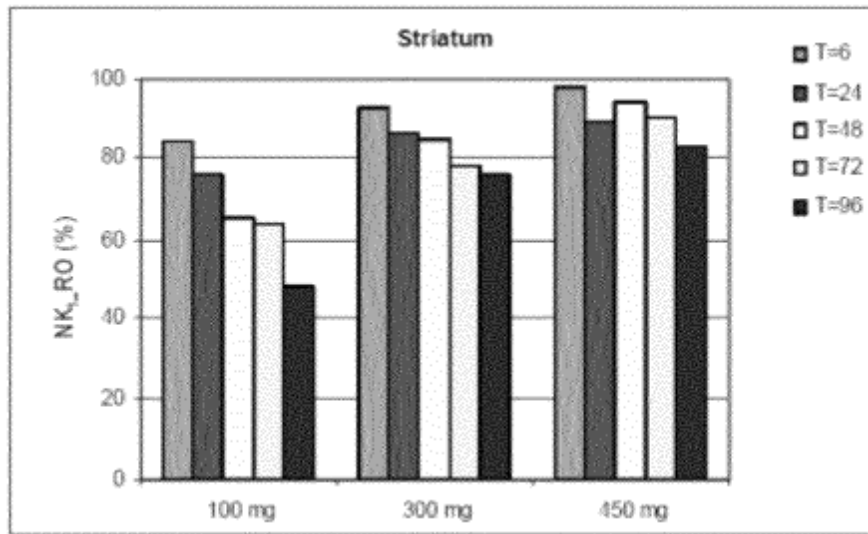


Figure 5 provides a bar graph that depicts the average NK receptor occupancy at 6, 24, 48, 72 and 96 hours after a single oral dose of 100, 300 and 450 mg. netupitant (N=2 for each dose) in striatum, as measured using positron emission topography. Ex. 1001, 6:58–62. With reference to Figure 5, the '826 patent states that 90% or higher occupancy (“close to the expected  $C_{max}$ ”) of the striatum receptors was reached with half of the subjects with a single oral dose. *Id.* at 16:44–48. Moreover, “[a]ll doses showed a relatively long duration of blockade of NK<sub>1</sub> receptors and the decline over time was dose dependent.” *Id.* at 16:52–53.

*ii. Illustrative Claims*

The Petition challenges all twenty-five claims of the '826 patent, of which claims 1 and 19 are independent. Claim 19 is illustrative and reproduced below.

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, 23:7–15 (paragraphing added).

*D. Asserted Grounds of Unpatentability*

Petitioner asserts the following grounds of unpatentability:

| Ground | Claim(s)<br>Challenged | 35 U.S.C. § <sup>1</sup> | Reference(s)/Basis                        |
|--------|------------------------|--------------------------|-------------------------------------------|
| 1      | 19, 22–23, 25          | 103                      | MASCC, <sup>2</sup> Hoffmann <sup>3</sup> |
| 2      | 19–20, 22–23, 25       | 103                      | MASCC, Bös <sup>4</sup>                   |

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<sup>1</sup> The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included amendments to 35 U.S.C. §§ 102 and 103 that became effective March 16, 2013. These amendments apply to applications (and patents issued thereon) that contained at any time—(A) a claim that has an effective filing date on or after March 16, 2013 or (B) a specific reference under 35 U.S.C. §§ 120, 121, or 365(c) to any patent or application that contains or contained at any time such a claim. *Id.* at § 3(n).

Based on the evidence of record, each of the asserted references is prior art to the challenged claims under either version of § 102. More specifically, each reference indicates that it was either patented or published more than one year before November 18, 2009. *See supra*, nn. 2–4. Thus, each reference is prior art under either version of section 102. *See pre-AIA* 35 U.S.C. § 102(b) (“A person shall be entitled to a patent unless . . . the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of the application for patent in the United States.”); *AIA* 35 U.S.C. § 102(a)(1) (“A person shall be entitled to a patent unless . . . the claimed invention was patented, described in a printed publication, or in public use, on sale, or otherwise available to the public before the effective filing date of the claimed invention.”). Nor does Patent Owner argue that any of the asserted references do not constitute prior art to the challenged claims. *See generally* Prelim. Resp.

<sup>2</sup> Ex. 1013, Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer (MASCC), *Prevention of chemotherapy- and radiotherapy-induced emesis: results of the 2004 Perugia International Antiemetic Consensus Conference*, 17 ANNALS OF ONCOLOGY 20 (2006).

<sup>3</sup> Ex. 1011, T. Hoffmann et al., *Design and synthesis of a novel, achiral class of highly potent and selective, orally active neurokinin-1 receptor antagonists*, 16 BIOORGANIC & MEDICINAL CHEMISTRY LETTERS 1362 (2006).

<sup>4</sup> Ex. 1014, US 6,297,375 B1, issued October 2, 2002.

| Ground | Claim(s)<br>Challenged  | 35 U.S.C. § <sup>1</sup> | Reference(s)/Basis                                          |
|--------|-------------------------|--------------------------|-------------------------------------------------------------|
| 3      | 19–23 & 25              | 103                      | MASCC, Bös, ALOXI <sup>5</sup>                              |
| 4      | 1–3, 8–10, 15–18,<br>24 | 103                      | Herrstedt, <sup>6</sup> Hoffman,<br>Hargreaves <sup>7</sup> |
| 5      | 1–3, 6–10, 15–18,<br>24 | 103                      | Herrstedt, Bös,<br>Hargreaves                               |
| 6      | 4–5                     | 103                      | Herrstedt, Bös,<br>Hargreaves, Herrington <sup>8</sup>      |
| 7      | 10–14                   | 103                      | Herrstedt, Bös,<br>Hargreaves, ALOXI                        |

Petitioner relies on a declaration of Stephen J. Peroutka, M.D., Ph.D. (Ex. 1009) to support its Petition. Patent Owner relies on a declaration of Rudolph M. Navari, M.D., Ph.D., F.A.C.P. (Ex. 2067) to support its Preliminary Response.

#### *E. Abbreviations*

|      |                                          |
|------|------------------------------------------|
| CINV | Chemotherapy-Induced Nausea and Vomiting |
| HEC  | Highly Emetogenic Chemotherapy           |
| MEC  | Moderately Emetogenic Chemotherapy       |

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<sup>5</sup> Ex. 1015, ALOXI (palonosetron HCl) Capsules, label (Revised 09/2008).

<sup>6</sup> Ex. 1010, J. Herrstedt et al., *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*, 101 BASIC & CLINICAL PHARMACOLOGY & TOXICOLOGY 143–150 (2007).

<sup>7</sup> Ex. 1012, R. Hargreaves, *Imaging Substance P Receptors (NK1) in the Living Human Brain Using Positron Emission Tomography*, 63(11) J. CLINICAL PSYCHIATRY 18–24 (2002).

<sup>8</sup> Ex. 1016, J.D. Herrington et al., *Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting*, 112 CANCER 2080–87 (March 7, 2008).

|                   |                            |
|-------------------|----------------------------|
| NK <sub>1</sub>   | Neurokinin-1               |
| 5-HT <sub>3</sub> | 5-Hydroxytryptamine Type 3 |

### III. ANALYSIS OF THE ASSERTED GROUNDS

#### A. *Level of Ordinary Skill in the Art*

In determining whether an invention would have been obvious at the time it was made, we consider the level of ordinary skill in the pertinent art at the time of the invention. *Graham v. John Deere of Kan. City*, 383 U.S. 1, 17 (1966). “The importance of resolving the level of ordinary skill in the art lies in the necessity of maintaining objectivity in the obviousness inquiry.” *Ryko Mfg. Co. v. Nu-Star, Inc.*, 950 F.2d 714, 718 (Fed. Cir. 1991). The “person having ordinary skill in the art” is a hypothetical construct, from whose vantage point obviousness is assessed. *In re Rouffet*, 149 F.3d 1350, 1357 (Fed. Cir. 1998).

Petitioner contends a person of ordinary skill in the art (“POSA”) would be someone “skilled in *one of* ‘clinical medicine, medical oncology, radiation oncology, oncology nursing, statistics, pharmacy, medical policy and decision making, and pharmacology.’” Pet. 8 (emphasis added) (quoting Ex. 1013, 20). Petitioner further contends:

In 2009, such professionals had advanced degrees in pharmacology, medicine, or allied fields, and would have worked in consultation with other specialists in these fields, and would have practical knowledge and experience about metabolism studies, in-vitro and in-vivo testing, formulation, and combination therapy.

Pet. 8. Petitioner also asserts that its expert “Dr. Peroutka is a pharmacologist familiar with the level of skill at the critical date.” *Id.* at 8.

Patent Owner “disagrees” with Petitioner’s contention “to the extent [it] does not require experience in the field of oncology, including work experience with cancer supportive care medications.” Prelim. Resp. 12.

Patent Owner also proposes its own definition, arguing:

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

*Id.* at 13. Patent Owner contends that Dr. Peroutka does not appear to have sufficient experience in the field of oncology to accurately opine from the perspective of a POSA as of the patent’s priority date. *Id.* at 13–14

At this stage, we need not resolve the parties’ dispute with regard to the requisite level of skill in the art, as our analysis would be the same under either party’s definition of a POSA. We note, however, that Petitioner’s definition seems to be overly broad insofar as it would only require the POSA to be skilled in one of several broad fields, including “statistics” and “medical policy and decision making,” that do not directly relate to the claimed subject matter. At the same time, we do not agree with Patent Owner that the POSA needs specific clinical experience in the field of oncology. The claimed subject matter relates to the treatment of a side-effect associated with cancer therapy (CINV), and not the cancer itself. We also recognize that the prior art and the ’826 patent itself reflect the level of

skill in the art. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“[T]he absence of specific findings on the level of skill in the art does not give rise to reversible error where the prior art itself reflects an appropriate level and a need for testimony is not shown.”).

We further find, based on the present record, that both parties’ experts are qualified to testify from the perspective of a POSA in this proceeding. *See* Ex. 1009 ¶¶ 1–7 (Dr. Peroutka’s qualifications); Ex. 2067 ¶¶ 8–15 (Dr. Navari’s qualifications); *Kyocera Senco Indus. Tools Inc. v. Int’l Trade Comm’n*, 22 F.4th 1369, 1377 (Fed. Cir. 2022) (“[T]o be qualified to offer expert testimony on issues from the vantage point of an ordinarily skilled artisan in a patent case, an expert must at a minimum possess ordinary skill in the art.”). Even if some specific experience with regard to the treatment of CINV is required, Dr. Peroutka appears to have published in that field. *See, e.g.*, Ex. 1020 at 10, (publication 16: article on “Combination antiemetics” in Cancer Treatment Reports); *id.* at 11 (publication 37: article on “Neurotransmitter receptor binding studies predict antiemetic efficacy and side effects” in Cancer Treatment Reports); *id.* at 13 (publication 51: article on “Chemotherapeutic agents do not interact with neurotransmitter receptors” in Cancer Chemotherapy and Pharmacology).

#### *B. Claim Construction*

In an *inter partes* review, claim terms “shall be construed using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b), including construing the claim in accordance with the ordinary and customary meaning of such claim as understood by one of ordinary skill in the art and the prosecution history pertaining to the patent.” 37 C.F.R. § 42.100(b).

Petitioner proposes construction for several claimed terms, which we address below. Pet. 9–10. Patent Owner does not dispute any of Petitioner’s constructions but argues that they are “unnecessary to resolve the parties’ disputes here.” Prelim. Resp. 14.

First, Petitioner proposes that “therapeutically effective amount” (recited in both independent claims) means: an amount sufficient to elicit the desired biological response. Pet. 9 (citing Ex. 1001, 7:55–57). The cited portion of the Specification clearly supports such a construction. Ex. 1001, 7:55–57 (“As used herein, ‘therapeutically effective amount’ refers to an amount sufficient to elicit the desired biological response.”). We adopt it.

Second, Petitioner proposes a construction for “minimum effective dose of dexamethasone.” Pet. 9. That term appears nowhere in the challenged claims. Accordingly, we do not interpret the term.

Finally, Petitioner proposes construing the following language appearing in claim 1: “administering to said patient on day one netupitant or a pharmaceutically acceptable salt thereof, in a therapeutically effective amount which *enters the systemic circulation, crosses the blood brain barrier and occupies at least 70% of neurokinin-1 (NK<sub>1</sub>) receptors in the striatum seventy-two hours after said administration.*” Pet. 9–10 (emphasis added). Specifically, Petitioner proposes that the italicized language, as introduced by the word “which,” denotes inherent properties (and not further limitations) resulting from the administering of the drug in a therapeutically effective amount. *Id.* On the instant record, with no argument to the contrary by Patent Owner, we agree with Petitioner. However, we do not explicitly address claim 1 below. Instead, the focus of our institution analysis is independent claim 19.

We do not perceive a need to construe expressly any other claim term of the '826 patent for purposes of determining whether to institute trial.

*C. Summary of Asserted References*

*i. Herrstedt (Ex. 1010)*

Herrstedt is an article published in the journal *Basic & Clinical Pharmacology & Toxicology* in 2007. Ex. 1010, 143. Patent Owner does not dispute that Herrstedt is prior art to the challenged claims.

Herrstedt is titled *Anti-Emetic Therapy in Cancer Chemotherapy: Current Status*. Ex. 1010, 1. It focuses on two classes of anti-emetics: serotonin<sub>3</sub>-receptor antagonists and NK<sub>1</sub> receptor antagonists. *Id.* at Abstr. According to Herrstedt:

The serotonin<sub>3</sub>-receptor antagonists, the first group of drugs developed specifically as anti-emetics, have significantly improved the prophylaxis of chemotherapy-induced emesis especially in combination with a corticosteroid. The improvement in the prophylaxis of nausea with this combination is however modest. A new group of anti-emetics, the neurokinin<sub>1</sub>-receptor antagonists, has now been developed, and the first drug, aprepitant, was marketed in 2003. Aprepitant increases the effect of a serotonin<sub>3</sub>-receptor antagonist plus a corticosteroid against acute emesis induced by highly or moderately emetogenic chemotherapy and aprepitant is also active in the protection against delayed emesis.

*Id.* Serotonin is also known as 5-hydroxytryptamine or 5-HT. Hence, “5-HT<sub>3</sub>-receptor antagonist” and “serotonin<sub>3</sub>-receptor antagonist” are synonymous. Ex. 1009 ¶79.

Herrstedt describes studies of combination therapy that demonstrated that the addition of aprepitant was beneficial to treat CINV. *See, e.g.*, Ex. 1010, 146. Further, “[t]he combination of aprepitant and oral

dexamethasone results in a two-time increase in the AUC [(i.e., area under the curve)] of dexamethasone indicating an inhibition of aprepitant on dexamethasone metabolism.” *Id.* at 147.

*ii. Hoffmann (Ex. 1011)*

Hoffmann is an article published in the journal *Bioorganic & Medicinal Chemistry Letters* in 2006. Ex. 1011, 1362. Patent Owner does not dispute that Hoffmann is prior art to the challenged claims.

Hoffmann teaches the discovery of netupitant as a “potent and orally active neurokinin-1 (NK<sub>1</sub>) receptor antagonist[.]” Ex. 1011, Abstract.

Hoffmann teaches that

recent clinical trials have demonstrated an important therapeutic application for NK<sub>1</sub> receptor antagonists in the control of cancer chemotherapy-induced nausea and vomiting and in the treatment of mood disorders such as anxiety and depression.[ Aprepitant] was the first NK<sub>1</sub> receptor antagonist to receive marketing approval. In March 2003, it was approved by the FDA for the treatment of chemotherapy-induced nausea and vomiting.

*Id.* at 1362. Like aprepitant, Hoffmann teaches that netupitant has favorable characteristics including high affinity at the NK<sub>1</sub> receptor and excellent oral NK<sub>1</sub>-antagonist activity. *Id.* at 1364. Hoffmann also tested netupitant in vivo and showed it potently inhibits NK<sub>1</sub> agonist-induced foot-tapping behavior in gerbils. *Id.* at 1365.

*iii. Hargreaves (Ex. 1012)*

Hargreaves is an article published in *The Journal of Clinical Psychiatry* in 2002. Ex. 1012. Patent Owner does not dispute that Hargreaves is prior art to the challenged claims.

Hargreaves is titled *Pathophysiology of Depression: The Emerging Role of Substance P*. Ex. 1012. Hargreaves teaches that “clinical studies have demonstrated that treatment with . . . aprepitant . . . significantly improves depression symptoms and reduces the incidence of chemotherapy-induced *nausea* and vomiting.” *Id.* at Abstr. Hargreaves describes using positron emission tomography (PET) “to establish the correlation between dose [of aprepitant], receptor occupancy, and the observed clinical effect.” *Id.* Hargreaves teaches an approximately 75% or greater NK<sub>1</sub>-receptor occupancy was associated with therapeutic doses that blocked emesis. *Id.* at 23 (Fig. 6B).

*iv. MASCC (Ex. 1013)*

MASCC is an article published in the *Annals of Oncology* in 2005. Ex. 1013. Patent Owner does not dispute that MASCC is prior art to the challenged claims.

MASCC is a review article written the Antiemetic Subcommittee of the Multinational Association of Supportive Care in Cancer, a multinational professional association, that provides recommendations for “antiemetic regimens to prevent emesis induced by high, moderate, low and minimal risk chemotherapy.” Ex. 1013, 20, 27. MASCC teaches aprepitant as

the first of a new class of drugs that selectively block the neurokinin-1 (NK1) neurotransmitter receptor, the binding site of the regulatory peptide Substance P. Aprepitant has been studied extensively for the prevention of cisplatin-induced emesis. Several phase II double-blind studies showed added antiemetic activity when combined with a 5-HT<sub>3</sub>-receptor antagonist plus dexamethasone[.]

Ex. 1013, 22. MASCC recommends combining aprepitant with a 5-HT<sub>3</sub>-receptor antagonist plus dexamethasone as the regimen of choice to prevent

acute vomiting and nausea following chemotherapy of high emetic risk. *Id.* MASCC discloses both oral and intravenous administration of the 5-HT<sub>3</sub> antagonist and dexamethasone, and oral administration of the NK<sub>1</sub> antagonist. *Id.* at 23–24.

v. *Bös (Ex. 1014)*

Bös is a U.S. patent issued on October 2, 2001. Patent Owner does not dispute that Bös is prior art to the challenged claims.

Bös explains that substance P is naturally present in the body, binds to NK<sub>1</sub> receptors, and is associated with numerous conditions. *Id.* at 1:17–67. Bös teaches using NK<sub>1</sub> antagonists to inhibit such conditions. *Id.* at 1:35–67. Of particular relevance here, Bös teaches using NK<sub>1</sub> antagonists for “mediation of the emetic reflex” and “for the treatment of motion sickness and for treatment [of] induced vomiting,” and, most relevantly, for “the reduction of cisplatin<sup>9</sup>-induced emesis.” *Id.* at 1:27, 1:59–64.

Although Bös does not refer to it as “netupitant,” Bös identifies and describes netupitant by its chemical formula, identifies it as “compound Ib,” and teaches that it has “valuable therapeutic properties as a highly selective antagonist of the Neurokinin 1 (NK-1, substance P).” *Id.* at 14:9–38. Bös tested netupitant in ferrets and observed that it “completely blocked the emesis induced by the emetogens.” *Id.* at 19:10–20.

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<sup>9</sup> Cisplatin is chemotherapeutic agent. *See* Ex. 1003, (“‘Highly emetogenic chemotherapy’ refers to chemotherapy having a high degree of emetogenic potential, and includes chemotherapy based on carmustine, *cisplatin*, cyclophosphamide > 1500 mg/m<sup>2</sup>, dacarbazine, dactinomycin, mechlorethamine, and streptozotocin.” (emphasis added)).

vi. *ALOXI (Ex. 1015)*

ALOXI is the 2008 revision for the FDA label for the drug ALOXI (palonosetron HCl capsules), which was originally approved in 2003.

Ex. 1015, 1. Patent Owner does not dispute that ALOXI is prior art to the challenged claims.

The label identifies ALOXI as a serotonin subtype 3 (5-HT<sub>3</sub>) antagonist indicated for “[m]oderately emetogenic cancer chemotherapy – prevention of acute nausea and vomiting associated with initial and repeat courses.” *Id.* ALOXI teaches an orally-administered capsule with 0.56 mg palonosetron HCl, equivalent to 0.5 mg of palonosetron. *Id.* at 3. ALOXI teaches administering the 0.5 mg capsules one hour prior to the start of chemotherapy. *Id.* at 2. ALOXI also teaches that in controlled clinical trials, the capsules were safely administered with chemotherapeutic agents, systemic corticosteroids (e.g., dexamethasone), and with other antiemetics/antinauseants. *Id.* Table 3 of ALOXI shows that 76.3% of patients administered the 0.5 mg oral capsule achieved a complete response in the first 0–24 hr period and 62.5% of patients achieved a complete response rate 24–120 hrs after chemotherapy. *Id.* at 4.

vii. *Herrington (Ex. 1016)*

Petitioner argues that Herrington is a journal article published in 2008, as shown on the face of Exhibit 1016. Pet. 13–14. Patent Owner does not dispute that Herrington is prior art to the challenged claims.

Herrington is titled *Randomized, Placebo-controlled, Pilot Study Evaluating Aprepitant Single Dose Plus Palonosetron and Dexamethasone for the Prevention of Acute and Delayed Chemotherapy-induced Nausea and Vomiting*. Ex. 1016, 1. Herrington describes clinical trials demonstrating

that a single dose on day-one of a therapeutically effective amount of NK<sub>1</sub> antagonist is as effective as multi-day administration of the same. *See* Ex. 1016, Abstr. (“From this pilot study of patients who were receiving palonosetron, aprepitant, and dexamethasone for highly emetogenic chemotherapy, a single dose of aprepitant displayed similar effectiveness compared with 3-day aprepitant.”).

*D. Rule 132 Declaration*

During prosecution, the Examiner asserted it would have been obvious to combine netupitant, palonosetron, and dexamethasone to treat CINV because the prior art taught an aprepitant/5-HT<sub>3</sub> antagonist/dexamethasone combination as the “standard of care,” and further identifies netupitant as an alternative NK<sub>1</sub> antagonist and palonosetron as an alternative 5-HT<sub>3</sub> antagonist. Ex. 1005, 328. In response, Patent Owner submitted a declaration under 37 C.F.R. § 1.132 (“Rule 132 Declaration”), in which the declarants Giorgia Rossi and Claudio Pietra provided certain *in vitro* and clinical data purporting to show unexpected results associated with the combination of palonosetron and netupitant. *Id.* at 341-350.

The Rule 132 Declaration indicates that unexpected synergy was observed from the combination with respect to the inhibition of substance-P. The declarants explained:

Because substance-P is the natural ligand for the NK-1 receptor, and palonosetron is a ligand for the 5-HT<sub>3</sub> receptor, we did not expect palonosetron to have any effect on substance-P response. However, we unexpectedly discovered that palonosetron inhibited the substance-P response. Even more surprisingly, we discovered that other established 5-HT<sub>3</sub> antagonists, specifically ondansetron and granisetron, did not inhibit substance-P response.

Rule 132 Decl., ¶ 12. The declaration includes the following data related to the concentration of substance-P required to induce  $\text{Ca}^{2+}$  mobilization (the “EC<sub>50</sub>”):

TABLE I

Inhibition of SP response in NC108-15 cells by netupitant (netu) and palonosetron (palo).

| SP + Antagonist(s)                 | EC <sub>50</sub> (μM) ± S.E.M. | n  |
|------------------------------------|--------------------------------|----|
| SP only                            | 2 ± 0.2                        | 38 |
| Plus netu (1 nM)                   | 2 ± 0.3                        | 3  |
| Plus netu (3 nM)                   | 5 ± 3                          | 3  |
| Plus netu (10 nM)                  | 10 ± 0.9                       | 3  |
| Plus netu (30 nM)                  | 40 ± 10 <sup>a</sup>           | 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 <sup>a</sup>            | 5  |
| Plus net (1 nM) plus palo (0.2 nM) | 120 ± 20 <sup>b</sup>          | 7  |
| Plus net (30 nM) plus palo (6 nM)  | 970 ± 150 <sup>c</sup>         | 5  |

*Id.* ¶ 17. As shown above, “[a]t concentrations where neither individual molecule increased the EC<sub>50</sub> of substance P, the combination of molecules increased the EC<sub>50</sub> of substance-P from 2 uM to 120 uM, a sixty-fold increase in the EC<sub>50</sub> of substance-P.” *Id.* ¶ 21. At higher concentrations, where the additive effect of the two ingredients was expected to be 66 μM (38 μM for netupitant + 28 μM for palonosetron), the declarants observed that the combination actually showed an EC<sub>50</sub> of 970 μM, a 500-fold increase compared to substance-P only. *Id.* ¶¶ 23.

In addition, the declarants “observed an unanticipated statistically significant effect against nausea from the combination of netupitant and palonosetron that has not previously been observed in clinical studies involving the combination of aprepitant with ondansetron or aprepitant with palonosetron.” *Id.* ¶ 28. The declaration provides the following table

including data from Patent Owner's clinical trials along with certain other comparative studies (with color coding added):

TABLE 2

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

\*Statistically Significant (p < 0.05)

<sup>nr</sup> Data Not Reported

<sup>ncs</sup> Non-Comparative Study; statistical significance not evaluated

<sup>a</sup> Helsinn Study NETU-07-07

<sup>b</sup> Helsinn Study NETU-08-18

<sup>c</sup> Warr *et al.* (2005) (Ref. D)

<sup>c1</sup> FDA-Approved Prescribing Information for Emend® (aprepitant) (results of two studies reported) (Ref. E)

<sup>d</sup> Herrington *et al.* (2008) (Ref. F)

<sup>e</sup> Grunberg *et al.* (2008) (Ref. G)

<sup>f</sup> Yeo *et al.* (2009) (Ref. H)

<sup>g</sup> Longo *et al.* (2012) (Ref. I)

*Id.* ¶ 32.

Based on the data reported above for highly emetogenic chemotherapy (HEC), the declarants stated that “the combination of aprepitant with palonosetron was not able to produce a statistically significant reduction in nausea or significant nausea in the HEC study reported in column 5 [color coded orange], while the combination of netupitant with palonosetron reported in column 1 [color coded green] was.”

*Id.* ¶ 34. With respect to moderately emetogenic chemotherapy (MEC), the declarants further concluded that “the combination of netupitant and palonosetron was able to protect 50% of the patients from nausea [shown in

column 3, color coded yellow] while the combination of aprepitant with palonosetron only protected 32% of the patients [shown in column 6, color coded pink].” *Id.* ¶ 35. Likewise, “[t]he combination of netupitant with palonosetron protected 75% of the MEC patients from significant nausea while the combination of aprepitant with palonosetron only protected 56% of the patients.” *Id.* ¶ 36.

The Examiner allowed the claims in the parent application in view of the synergy and unexpected results shown in the Rule 132 Declaration. Ex. 1005, 369.

*E. Ground 1: Obviousness of Claims 19, 22–23, 25 over MASCC and Hoffmann*

Petitioner asserts that claims 19, 22–23, and 25 are unpatentable under 35 U.S.C. § 103 as obvious over the combination of MASCC and Hoffmann. Pet. 17–23. To support its contentions, Petitioner provides a detailed discussion explaining how each claim limitation is disclosed in the combination of MASCC and Hoffmann. *Id.* (citing Ex. 1009, 127–64). Petitioner’s contentions are supported by the declaration of Dr. Peroutka. Ex. 1009, 127–64.

In view of the following, we determine that Petitioner has demonstrated a reasonable likelihood of prevailing as to independent claim 19 on this ground. Our conclusion with regard to this ground is sufficient for institution of all of the grounds identified in the Petition. *See SAS Inst., Inc. v. Iancu*, 584 U.S. 357, 370 (2018); *PGS Geophysical AS v. Iancu*, 891 F.3d 1354, 1360 (Fed. Cir. 2018) (interpreting the statute to require “a simple yes-or-no institution choice respecting a petition, embracing all challenges included in the petition”).

*i. Petitioner's Contentions*

With regard to independent claim 19, Petitioner contends that it would have been obvious to substitute netupitant for aprepitant in MASCC's three-drug regimen that combines administering an NK<sub>1</sub> antagonist (aprepitant), a 5-HT<sub>3</sub> antagonist (palonosetron), and dexamethasone for treating both nausea and vomiting for acute and delayed CINV following MEC or HEC. Pet. 17; *see also* Ex. 1013, 22 ("Therefore, to prevent acute vomiting and nausea following chemotherapy of high emetic risk, a three-drug regimen including single doses of a 5-HT<sub>3</sub>-receptor antagonist, dexamethasone and aprepitant given before chemotherapy is recommended (MASCC level of consensus: high; MASCC level of confidence: high)."); Ex. 1009 ¶ 131. As to the choice of 5-HT<sub>3</sub> antagonist, Petitioner contends that MASCC teaches administering a therapeutically-effective amount of palonosetron. Pet. 20 (citing Ex. 1013, 24).

Petitioner acknowledges that MASCC teaches aprepitant, not netupitant, but contends that "Hoffmann teaches netupitant is an 'excellent' alternative to aprepitant." Pet. 19 (citing Ex. 1011, Abst. ("The evaluation of this [NK<sub>1</sub> antagonist] class is briefly outlined, leading to the identification of netupitant[, one of] two new proprietary chemical entities with high affinity and excellent CNS penetration."); Ex. 1009 ¶ 135). Petitioner contends that "Hoffmann provides ample reason to substitute netupitant in MASCC's 3-drug regimen with palonosetron and dexamethasone and reasonably expect success based on netupitant's excellent efficacy." *Id.*, *see also* Ex. 1009 ¶ 136 ("Hoffmann identified netupitant as an attractive NK<sub>1</sub> receptor antagonist for replacing aprepitant.").

Based on the arguments and evidence of record at this stage, we find that Petitioner has shown a reasonable likelihood of establishing that at least claim 19 would have been obvious over the combination of MASCC and Hoffmann. We are unpersuaded by Patent Owner’s arguments to the contrary, which we address below. *See* Prelim. Resp. 15–41.

*ii. Patent Owner’s Contentions*

*a. Whether Petitioner Applies the Wrong Legal Framework*

To begin, Patent Owner argues that the Petition “Applies the Wrong Legal Framework” because it “begins with [Patent Owner]’s invention, and then works backwards by cobbling together the prior art so as to arrive at the claimed invention[.]” Prelim. Resp. 15. Thus, Patent Owner argues, Petitioner’s “approach is emblematic of impermissible hindsight and must fail for this reason alone.” *Id.* at 16.

Patent Owner’s specific critique in this regard is that the Petition analyzes *only* whether the claimed invention would have been obvious and not whether *other* methods of treating CINV that are not covered by the challenged claims also would have been obvious. *See id.* at 18 (“Contrary to [Petitioner]’s assertions, the obviousness question here cannot be narrowly framed to focus only on whether it would have been obvious to a POSA substitute netupitant for aprepitant in the three-drug regimen.”). According to Patent Owner, “A POSA in November 2009 Had Many Potential Pathways for Attempting to Develop an Improved Treatment for CINV That Allowed for Control of Nausea.” *Id.* at 19. “For example, [Patent Owner argues,] one possible pathway for a POSA to consider would have been adding a *fourth* drug to the three-drug regimen to control nausea instead of substituting for individual drugs (*e.g.*, aprepitant) in that regimen.” *Id.* at

20–21; *see also id.* at 22 (“For example, a POSA could have considered adding other drugs, like gabapentin and cannabinoids, from other, different drug classes to the three-drug regimen for controlling nausea.”), 24 (“[Petitioner], however, fails to consider any of the[] alternative NK-1 receptor antagonists that were known by November 2009—let alone their advantages or shortcomings—and instead contends that a POSA would have zeroed in on netupitant.”). Patent Owner concludes that Petitioner’s “lack of consideration of these alternate paths, coupled with its singular focus on netupitant, underscores that its obviousness analysis is infected by impermissible hindsight.” *Id.* at 22.

We are not persuaded by these arguments. The fact that there may have been other solutions to the problem of treating CINV does not suggest that the claimed combination, as proposed by Petitioner, is non-obvious. The law expressly contemplates that multiple solutions can be obvious. Indeed, an inferior solution can be obvious even when a superior solution is also available. *See In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012) (“[J]ust because better alternatives exist in the prior art does not mean that an inferior combination is inapt for obviousness purposes.”). Further, obviousness “does not require that the motivation be the *best* option, only that it be a *suitable* option from which the prior art did not teach away.” *Par Pharm., Inc. v. TWI Pharms., Inc.*, 773 F.3d 1186, 1197–98 (Fed. Cir. 2014).

*b. Whether Petitioner Fails to Show That a POSA Would Have Chosen Netupitant*

Patent Owner contends that Petitioner “fails to show a POSA would have focused on using netupitant for a potential CINV treatment over other

NK-1 receptor antagonists.” Prelim. Resp. 23. Specifically, Patent Owner contends that Petitioner “fails to explain why a POSA would have immediately wanted to ‘swap out’ part of the triple therapy for CINV (aprepitant) that was known to be extremely effective against vomiting,” especially in view of all the other “alternative NK-1 receptor antagonists that were known by November 2009.” *Id.* at 23–24 (citing Ex. 2067 ¶¶ 98–106). Here, Patent Owner asserts that Hoffmann teaches netupitant as “one of 31 NK-1 receptor antagonists” but contends that Petitioner did not explain why a POSA would have selected netupitant to the exclusion of the other compounds known in the prior art. *Id.* at 25 (citing Ex. 1011, 1364; Ex. 1014, Ex. 2067 ¶¶ 100–106).

On the current record, we are unpersuaded by Patent Owner’s arguments because Patent Owner fails to rebut Petitioner’s reason for substituting netupitant for aprepitant. Patent Owner does not dispute that aprepitant and netupitant were both known NK<sub>1</sub> 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.”).

Further, the Petition identifies explicit teachings by Hoffman that supports the obviousness of using netupitant in lieu of aprepitant in MASCC’s three-drug regimen for treating CINV. Pet. 17–19. First, Hoffman teaches that NK<sub>1</sub> antagonists are useful for the treatment of CNIV. Ex. 1011, 1362. Second, Hoffman specifically identifies and describes netupitant as an NK<sub>1</sub> antagonist and teaches that it has “high affinity and

excellent CNS penetration” as demonstrated by its ability to “pharmacologically block central NK<sub>1</sub> receptors” in an in vivo animal model. *Id.* at 1364–1364; *see also* Ex. 1009 ¶ 160 (“Hoffmann explains, netupitant was shown ‘to potently inhibit NK1 agonist-induced foot tapping . . . after oral administration’ which was indicative of successful NK1 receptor antagonism, and also identified netupitant as having ‘[e]xcellent oral antagonist activity.’”).

*c. Whether Petitioner’s “Obvious to Try” Argument Fails*

Patent Owner contends that Petitioner “fails to provide sufficient evidence from which the Board can find that . . . ‘substituting netupitant and palonosetron’ in the three-drug combination would have been ‘obvious to try,’ and a POSA would have ‘reasonably expect[ed] success’ in doing so.” Prelim. Resp. 28. Patent Owner asserts that conclusory statements represent the entirety of Petitioner’s argument, which is insufficient as a matter of law to support Petitioner’s obviousness challenge. *Id.* Specifically, Patent Owner contends that Petitioner

has not provided any analysis establishing that the possible options available to a POSA in November 2009 were finite, small, or easily traversed. There are entirely different classes of drugs (e.g., benzodiazepines, antiepileptics, antipsychotics, cannabinoids, corticosteroids, and dopamine antagonists) and numerous compounds within those classes that a POSA could have considered. (Ex. 2067 at ¶ 25.) Moreover, numerous NK-1 receptor antagonists were in various stages of development by many different pharmaceutical companies at that time, which would have also been known to a POSA. (Ex. 2067 at ¶ 41.) Azurity does not (and cannot) explain how these many potential pathways could conceivably constitute a “finite, small, or easily traversed” class that would have been obvious to try.

Prelim. Resp. 29.

In *In re Kubin*, the court “outlined two classes of situations where ‘obvious to try’ is erroneously equated with obviousness under § 103” to differentiate between proper and improper applications of the “obvious to try” rationale. 561 F.3d 1351, 1359 (Fed. Cir. 2009), citing *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988). In the first class of cases,

what would have been “obvious to try” would have been to vary all parameters or try each of numerous possible choices until one possibly arrived at a successful result, where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful.

*Id.* In the second class,

what was “obvious to try” was to explore a new technology or general approach that seemed to be a promising field of experimentation, where the prior art gave only general guidance as to the particular form of the claimed invention or how to achieve it.

*Id.*

We are not persuaded by Patent Owner’s arguments that either erroneous situation is present in the instant case. Here, Patent Owner takes an expansive view of the prior art that is beyond the scope of Petitioner’s obviousness challenge based on the combination of MASCC and Hoffmann. That is, in an attempt to establish more than a finite number of possible options from which “[a POSA] would have had a reason to select the route that produced the claimed invention,” Patent Owner references entire drug categories and numerous other NK<sub>1</sub> receptor antagonists as options or potential pathways for treating CINV. Prelim. Resp. 29; *see also* Ex. 2067 ¶¶ 25, 41 (Dr. Navari identifying classes of antiemetic agents and “numerous” other NK<sub>1</sub> receptor antagonists targeting various neuroreceptors

as potentially being involved in CINV). What is relevant to the instant analysis, however, is whether the specific teachings of MASCC and Hoffmann would have suggested to a POSA a three-drug regimen comprising netupitant and palonosetron in the treatment of CINV with a reasonable expectation of success.

To that point, our reviewing court instructs that a conclusion of obviousness is appropriate where the prior art “contain[s] *detailed enabling methodology* for practicing the claimed invention, a suggestion to modify the prior art to practice the claimed invention, and evidence suggesting that it would be successful.” *Kubin*, 561 at 1360 (emphasis in original). Here, MASCC provides detailed information regarding a method of using the combination of an NK<sub>1</sub> antagonist, a 5-HT<sub>3</sub> antagonist, and dexamethasone for treating both nausea and vomiting for acute and delayed CINV following MEC or HEC. Pet. 17; Ex. 1013, 22. MASCC also specifically suggests palonosetron as the preferred choice of 5-HT<sub>3</sub> antagonist, as recited in claim 19. Pet. 20 (citing Ex. 1013, 24 (“Palonosetron is a 5-HT<sub>3</sub>-receptor antagonist that has a longer half-life and more avid receptor binding than the other 5-HT<sub>3</sub> receptor antagonists.”)). Finally, as for choice of NK<sub>1</sub> antagonist, Hoffmann identifies netupitant as a promising candidate. Ex. 1011, Abst.

These references, which together teach each element of claim 19, are unlike prior art that gives “no direction as to which of many possible choices is likely to be successful” or “only general guidance as to the particular form of the claimed invention or how to achieve it.” *O’Farrell*, 853 F.2d at 903. At this stage of the proceeding, we credit the Peroutka Declaration as establishing sufficient reasons, for purposes of institution, that the

combination of MASCC and Hoffmann would have been obvious to a person of ordinary skill in the art with a reasonable expectation of success. *See, e.g.*, Ex. 1009 (¶¶ 77–84, 127–143); *see also O’Farrell*, 853 F.2d at 903–904 (“Obviousness does not require absolute predictability of success[,] . . . all that is required is a reasonable expectation of success.”).

*d. Whether Petitioner Fails to Demonstrate Any Reasonable Expectation of Success by a POSA*

Patent Owner argues that Petitioner “provides no evidence that a POSA would have reasonably expected the netupitant-based three-drug regimen to be effective at treating [both] nausea and vomiting.” Prelim. Resp. 30 (emphasis omitted). More specifically, Patent Owner contends that MASCC’s three-drug regimen failed to treat nausea and Petitioner “offers no evidence that incorporating netupitant in place of aprepitant would have provided a different result.” *Id.* at 31 (citing Ex. 2067 ¶¶ 107–109 (“None of [Dr. Peroutka’s] cited references (Bös and Hoffmann) discuss netupitant’s effect on nausea.”)). Thus, according to Patent Owner, Petitioner’s “conclusory allegations regarding a reasonable expectation of success are insufficient as a matter of law.” *Id.*

We are not persuaded by Patent Owner’s arguments. Patent Owner erroneously frames the legal requirement for a reasonable expectation of success. Petitioner must show that a POSA would have had a reasonable expectation of success in combining the prior art teachings in the manner claimed. *See Life Techs. Inc. v. Clontech Labs. Inc.*, 224 F.3d 1320, 1326 (Fed. Cir. 2000) (“Reasonable expectation of success is assessed from the perspective of the person of ordinary skill in the art. That the inventors were ultimately successful is irrelevant to whether one of ordinary skill in the art,

at the time the invention was made, would have reasonably expected success.”). Thus, Petitioner must show that a POSA would have had a reasonable expectation of success in modifying MASCC’s combination therapy for treating CINV by substituting netupitant for aprepitant. Framed properly, the record evidence shows adequate support for a reasonable expectation of success. The POSA would need to only substitute one known NK<sub>1</sub> antagonist for another. *See* Ex. 1011, Abst. (Hoffmann teaching netupitant as a potent and orally active NK<sub>1</sub> receptor antagonist having “excellent CNS penetration.”); *see also* Ex. 1009 ¶ 136 (“[A] POSA would have had an extremely high likelihood of succeeding in substituting netupitant for aprepitant for antiemetic combination therapy because both compounds are NK<sub>1</sub> receptor antagonists and are intended to achieve their purpose (to decrease nausea and vomiting) through the very same mechanism (NK<sub>1</sub> receptor antagonism) when administered prior to chemotherapy.”).

*e. Whether Patent Owner’s Evidence of Unexpected Synergy Further Confirms Nonobviousness*

Patent Owner also reiterates and emphasizes the unexpected evidence results it submitted during prosecution as evidence of non-obviousness. Prelim. Resp. 31–35. Patent Owner points to the synergy between the netupitant and palonosetron on substance P, as shown in Table 1 of the Rule 132 Declaration. *Id.* at 32–33. Patent Owner contends that this data indicates a greater clinical impact on the control of nausea, when netupitant and palonosetron are administered together, as compared to the sum of their effects when administered separately. *Id.* at 33. Patent Owner argues that Petitioner’s contention that the combination of netupitant and palonosetron

had no better effect on nausea compared to other known combinations of 5-HT<sub>3</sub> and NK<sub>1</sub> receptor antagonists is not supported by any scientific evidence or data. *Id.* at 33–34. Patent Owner also argues that controlled clinical trials showed that aprepitant combined with 5-HT<sub>3</sub> antagonists (ondansetron or palonosetron) did not provide statistically significant relief for “nausea” or “significant nausea,” as compared to standard therapy, for both HEC and MEC patients. *Id.* at 34.

Patent Owner further contends that it did not misrepresent any data during prosecution, and the majority of this data was readily available through the same public documents cited in the Rule 132 Declaration. *Id.* at 35–41. Patent Owner contends that the data from the Emend label and other industry publications all confirmed there was no improved efficacy on nausea by aprepitant. *Id.* at 36–38 (citing Ex. 1016, 2086 (“According to its package insert, aprepitant fails to demonstrate improved efficacy over placebo for the prevention of nausea (overall and significant nausea) in acute [(Day 1)] or delayed phases [(Days 2-5)]” after chemotherapy.); Ex. 1048,<sup>10</sup> 534 (“Assessment of [Functional Living Index-Emesis (FLIE)] revealed that . . . there was no difference in the nausea domain” in a study “compar[ing] the efficacy of aprepitant-based antiemetic regimen and standard antiemetic regimen for the prevention of [CINV].”); *see also* Ex. 2067 ¶ 122.

Moreover, with regard to the data from Patent Owner’s internal studies presented in columns 1 and 3 of Table 2 in the Rule 132 Declaration, Patent

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<sup>10</sup> Ex. 1048, Yeo et al., *A randomized study of aprepitant, ondansetron and dexamethasone for chemotherapy-induced nausea and vomiting in Chinese breast cancer patients receiving moderately emetogenic chemotherapy*, 113 BREAST CANCER RESEARCH AND TREATMENT 529 (2009).

Owner states that, “[i]f the Office had wanted to evaluate the underlying data, they could have simply asked [Patent Owner] to provide it, and [Patent Owner] would have obliged without issue.” *Id.* at 39–40.

Petitioner preemptively addresses the alleged unexpected results associated with netupitant based on the data included in the specification and in the Rule 132 Declaration submitted during prosecution of the parent application. *Id.* at 58–70. Petitioner contends that the asserted unexpected properties for netupitant were already present for aprepitant, including efficacy for nausea. *Id.* at 59–61. Petitioner points out that the label for Emend (Ex. 1030) shows a reduction of nausea, particularly significant nausea. Pet. 60–61. Although statistical significance was not calculated for nausea parameters, Petitioner points out that the “complete protection” value defined as an efficacy endpoint includes a metric based on a “maximum nausea visual analogue scale [VAS] score <25 mm on a 0 to 100 mm scale.” *Id.* (citing Ex. 1030, 7). Petitioner also points out that the Emend label reports an overall improvement from 66% to 73% for significant nausea in a first study, and that a higher proportion of patients reported minimal or no impact on nausea and vomiting in a second study. *Id.* at 61. Petitioner also points out that Campos (Ex. 1023) discloses aprepitant’s therapeutic benefit for nausea during both the acute and delayed phases of CINV. *Id.* at 63.

Petitioner further contends that, despite Patent Owner’s representations, Example 5 of the patent Specification shows that aprepitant had an effect on nausea that was comparable to netupitant. *Id.* at 61–62. In arguing otherwise during prosecution, Petitioner contends that Patent Owner misleadingly excised information from Table 6’s larger data set, and that Example 5 was never designed to compare netupitant against aprepitant. *Id.*

Likewise, Petitioner contends that Patent Owner's response to the Examiner "materially altered" the table taken from the Rule 132 Declaration without noting the alterations. *Id.* at 64. In particular, Petitioner asserts that the declaration excluded data from the studies purporting to show a similar effect for ondasetron + aprepitant versus palonsetron + netupitant (columns 4 and 7), instead indicating that the data was "not reported." *Id.* at 65. Furthermore, Petitioner points out that the data regarding aprepitant cited in the Specification's Table 6 and in the Rule 132 Declaration came from a different study by Grunberg (Ex. 1035) with a different design, including differences in dosing, that precluded making a direct comparison to netupitant. *Id.* at 66. Even assuming that the comparison to the aprepitant + ondansetron combination was appropriate, Petitioner points out that the data showed only marginal improvement for the highest netupitant dose and that aprepitant actually showed an improved anti-nausea effect compared to lower netupitant doses. *Id.* at 62. Petitioner contends there is no unexpected synergy between netupitant and palonosetron, nor is there a nexus between the alleged synergy and the claimed invention. *Id.* at 68.

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

*Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014) (“[E]vidence of unexpected results must establish that there is a difference between the results obtained and those of the closest prior art.”). Furthermore, while Table 2 of the Rule 132 Declaration does include comparisons to the palonosetron + aprepitant combination, those comparative results were obtained from different studies (by Grunberg and Longo), and it is not clear that the criteria used in those studies were the same criteria used in Patent Owner’s clinical studies administering the combination of palonosetron + netupitant. Moreover, contrary to Patent Owner’s contention that the prior art did not recognize anti-nausea properties for aprepitant, Campos demonstrated reduced nausea scores for the combination of aprepitant (MK-869) + granisetron + dexamethasone. Ex. 1023, 1763–1764. As such, it is not clear that a reduction in nausea could be considered an unexpected property unique to netupitant. That said, however, here, as in most cases, an analysis of objective evidence of nonobviousness is best made on a complete trial record, and not upon the incomplete record presented at the institution stage. The parties are invited to address this issue during trial.

#### IV. CONCLUSION

After considering the evidence and arguments presented in the current record, we determine that Petitioner has demonstrated a reasonable likelihood of success in establishing that at least one challenged claim of the ’826 patent is unpatentable. We therefore institute trial on all challenged claims under the grounds raised in the Petition. 37 C.F.R. § 42.108(a); *SAS*, 138 S. Ct. at 1355.

Our determination in this Decision is not a final determination on the patentability of the challenged claims. Thus, we do not resolve at this stage any disputed factual issues necessary to determine whether sufficient evidence supports Petitioner’s contentions by a preponderance of the evidence in the final written decision. *See TriVascular, Inc. v. Samuels*, 812 F.3d 1056, 1068 (Fed. Cir. 2016) (noting in the context of an *inter partes* review that “there is a significant difference between a petitioner’s burden to establish a ‘reasonable likelihood of success’ at institution, and actually proving invalidity by a preponderance of the evidence at trial”) (quoting 35 U.S.C. § 314(a) and comparing § 316(e)).

Patent Owner is cautioned that any argument not raised in a timely Patent Owner Response to the Petition, or as permitted in another manner during trial, shall be deemed waived even if asserted in the Preliminary Response. *See In re Google Tech. Holdings LLC*, 980 F.3d 858, 862–64 (Fed. Cir. 2020) (holding an argument forfeited when not timely raised before the Board); *In re NuVasive, Inc.*, 842 F.3d 1376, 1380–81 (Fed. Cir. 2016) (holding Patent Owner waived an argument addressed in the Preliminary Response by not raising the same argument in the Patent Owner Response).

## V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED, pursuant to 35 U.S.C. § 314(a), an *inter partes* review of claims 1–25 of the ’826 patent is instituted with respect to the grounds set forth in the Petition; and

FURTHER ORDERED, pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4(b), that the *inter partes* review of the ’826 patent shall commence on

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the entry date of this Order, and notice is hereby given of the institution of a trial.

IPR2025-00945  
Patent 8,623,826 B2

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