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Paper No. 10
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UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,
Petitioner,

v.

NOVO NORDISK A/S,
Patent Owner.

IPR2023-00724
Patent 10,335,462 B2

Before JOHN G. NEW, SUSAN L. C. MITCHELL, and ROBERT A. POLLOCK, *Administrative Patent Judges.*

MITCHELL, *Administrative Patent Judge*.

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

I. INTRODUCTION

Mylan Pharmaceuticals Inc. ("Petitioner") filed a Petition (Paper 1, "Pet."), seeking *inter partes* review of claims 1–10 U.S. Patent No. 10,335,462 B2 (Ex. 1001, "the '462 patent"). Novo Nordisk A/S ("Patent Owner") filed a Preliminary Response. Paper 6 ("Prelim. Resp.").

In its Preliminary Response, Patent Owner requests that the Board exercise its discretion to deny institution under 35 U.S.C. §§ 325(d) and 314(a). *See* Prelim. Resp. 59–67. Patent Owner also raises challenges to the merits of the grounds in the Petition. *Id.* at 14–59.

After considering the arguments and evidence presented at this stage of the proceeding, we are persuaded that Petitioner has demonstrated a reasonable likelihood that it would prevail with respect to at least one claim challenged in the Petition. *See* 35 U.S.C. § 314(a). We also decline to exercise our discretion to deny institution under 35 U.S.C. §§ 325(d) or 314(a). Accordingly, we institute *inter partes* review.

II. BACKGROUND

A. Real Parties in Interest

Petitioner identifies Mylan Pharmaceuticals Inc., Mylan Inc., and Viatris Inc. as real parties in interest. *See* Pet. 1. Patent Owner identifies itself as the real party in interest, but also lists exclusive licensee Novo Nordisk Inc. *See* Paper 4, 1.

DR. REDDY'S LABORATORIES, INC.
IPR2024-00009
Ex. 1097, p. 2 of 41

B. Related Matters

Petitioner and Patent Owner identify the following litigations as related matters, the first three of which involve Petitioner as a defendant. Pet. 1–2; Paper 4, 1–2.

1. *Novo Nordisk Inc. v. Mylan Pharms. Inc.*, No. 22-cv-01040-CFC (D. Del.)
2. *In re Ozempic (Semaglutide) Patent Litigation*, No. 22-md-3038-CFC (D. Del.)
3. *Novo Nordisk Inc. v. Mylan Pharms. Inc.*, No. 22-cv-00023 (N.D.W. Va.)
4. *Novo Nordisk Inc. v. Aurobindo Pharma USA, Inc.*, No. 1:22-cv-00295 (D. Del.) (dismissed on March 28, 2022)
5. *Novo Nordisk Inc. v. Rio Biopharmaceuticals, Inc.*, No. 1:22-cv-00294 (D. Del.)
6. *Novo Nordisk A/S v. Sun Pharm. Indus. Ltd.*, No. 1:22-cv-00296 (D. Del.)
7. *Novo Nordisk Inc. v. Zydus Worldwide DMCC*, No. 1:22-cv-00297 (D. Del.)
8. *Novo Nordisk Inc. v. Dr. Reddy's Laby's Ltd.*, No. 1:22-cv-00298 (D. Del.)
9. *Novo Nordisk Inc. v. Alvogen, Inc.*, No. 1:22-cv-00299 (D. Del.)

C. The '462 Patent

The '462 patent issued on July 2, 2019, and is a continuation of an application filed June 21, 2013, now U.S. Patent No. 9,764,003, and claims priority from two provisional applications and two foreign applications, the

earliest of which was filed on July 1, 2012. Ex. 1001, codes (30), (45), (60), (63); 1:6–15.

The ’462 patent relates to “use of long-acting GLP-1 peptides in certain dosage regimes for the treatment of type 2 diabetes, obesity, etc.” Ex. 1001, Abstr. The ’462 patent further describes one embodiment as follows:

> In one embodiment the invention relates to a method for a) reduction of HbA_{1c}; b) prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or c) prevention or treatment of obesity, reducing body weight and/or food intake, or inducing satiety; wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist i) has a half-life of at least 72 hours, wherein said half-life optionally is determined by Assay (II); ii) is administered to an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and iii) is administered once weekly or less often.

Ex. 1001, 1:31–44.

The sole example provided in the ’462 patent describes administering semaglutide, “a unique acylated GLP-1 peptide with a half-life of 160 hours,” in order “to investigate HbA_{1c} dose-response of once-weekly doses of semaglutide (five dose-levels) in subjects with type 2 diabetes. Safety, tolerability and pharmacodynamics of semaglutide versus placebo and open-label once-daily liraglutide were also investigated.” Ex. 1001, 20:66–21:5.

Figure 1 set forth below shows the change in HbA_{1c} from baseline at week 12 for Example 1. Ex. 1001, 22:5–7.

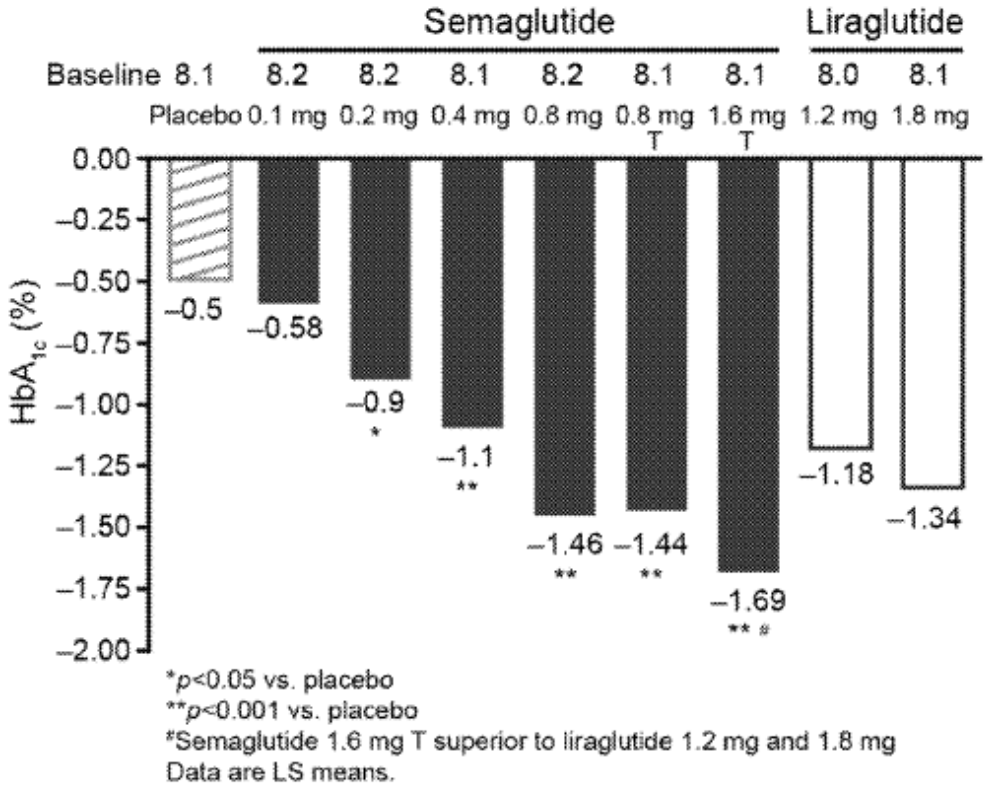

Fig. 1

The analysis of the results in Figure 1 set forth above shows "semaglutide (≥0.2 mg) dose-dependently reduced HbA_{1c} from baseline (FIG. 1), and increased the likelihood of achieving HbA_{1c}<7% (p<0.05 vs. placebo for doses ≥0.2 mg)." Ex. 1001, 22:2–5. The example also showed that "[b]ody weight was dose-dependently reduced from base-line by up to 4.8 kg vs. placebo 1.2 kg (p<0.1 for doses 13.8 mg).

The '462 patent concludes:

> Over 12 weeks, semaglutide dose-dependently reduced HbA_{1c} and body weight. The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg. No semaglutide safety concerns were

> identified. Dose escalation was not a major focus of this trial and it will be optimized in future clinical trials.

Ex. 1001, 23:18–26.

D. Challenged Claims

The Petition challenges claims 1–10. *See* Pet. 4. Challenged claim 1 is the sole independent claim. *See* Ex. 1001, 35:42–44. Claim 1 is illustrative of the challenged claims. Claim 1 is reproduced below.

> 1. A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.

Ex. 1001, 35:42–44.

E. Asserted Grounds of Unpatentability

Petitioner asserts the following grounds of unpatentability:

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1–3	102(a), (e)	WO421[2]
1–3	102(b)	Lovshin[3]
1–10	103(a)	WO421, ’424 publication[4]

[1] The Leahy-Smith America Invents Act, Pub. L. No. 112-29, 125 Stat. 284 (2011) (“AIA”), included revisions to 35 U.S.C. §§ 102 and 103 that became effective on March 16, 2013, after the filing of the applications to which the ’462 patent claims priority. Therefore, we apply the pre-AIA versions of Sections 102 and 103.
[2] Thomas Klein et al., WO 2011/138421 A1, published November 10, 2011 (Ex. 1011, “WO421”).
[3] Julie A. Lovshin and Daniel J. Drucker, *Incretin-based therapies for type 2 diabetes mellitus*, 5 NATURE REVIEWS/ENDOCRINOLOGY 262–269 (2009) (Ex. 1012, “Lovshin”).
[4] Tina B. Pedersen et al., US 2007/0010424 A1, published Jan. 11, 2007 (Ex. 1016, “’424 publication”).

Claim(s) Challenged	35 U.S.C. §[1]	Reference(s)/Basis
1–10	103(a)	WO537,[5] Lovshin
1–10	103(a)	NCT657,[6] NCT773,[7] '424 publication

Pet. 5.

Petitioner further relies on the declarations of John Bantle, M.D. (Ex. 1003), William J. Jusko, Ph.D. (Ex. 1005), and Paul Dalby, Ph.D. (Ex. 1007) submitted with the Petition.

Before turning to our analysis of these grounds, we address Patent Owner's arguments that, notwithstanding the merits of Petitioner's grounds, we should exercise discretion to deny institution under 35 U.S.C. §§ 325(d) and 314(a).

III. DISCRETION UNDER 35 U.S.C. § 325(d)

Patent Owner asserts that we should exercise our discretion under Section 325(d) to deny institution because:

> Petitioner relies on art that was expressly applied during prosecution of the '462 and its parent ('003), is cited on the '462's face, or is cumulative of such art. Petitioner further fails to address the multiple prior-art-based rejections issued during

[5] Jesper Lau et al., WO 2006/097537 A2, published Sept. 21, 2006 (Ex. 1015, "WO537").
[6] ClinicalTrials.gov, Clinical Trial No. NCT00696657, *A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide*, http://web.archive.org/web/20111020123620/https://clinicaltrials.gov/ct2/show/NCT00696657 (Ex. 1013, "NCT657").
[7] ClinicalTrials.gov, Clinical Trial No. NCT00851773, *Safety, Tolerability, and Profile of Action of Drug in the Body of NN9536 in Healthy Male Japanese and Caucasian Subjects*, https://web.archive.org/web/20090911011536/https://clinicaltrials.gov/ct2/show/NCT00851773 (Ex. 1014, "NCT773").

> '003's prosecution and misstates the Examiners' findings during '462's prosecution, and thus also fails to meet its burden to show Examiner error material to the challenged claims' patentability.

Prelim. Resp. 59.

Section 325(d) provides that the Director may elect not to institute a proceeding if the challenge to the patent is based on prior art or arguments previously presented to the Office. The statute states, in pertinent part, "[i]n determining whether to institute . . . the Director may take into account whether, and reject the petition . . . because, the same or substantially the same prior art or arguments previously were presented to the Office." 35 U.S.C. § 325(d).

The question of whether the petition presents art or arguments that are "the same or substantially the same" as art or arguments previously presented to the Office is a factual inquiry, which may be resolved by reference to the factors set forth in *Becton, Dickinson*.[8] The precedential section of that decision sets forth the following non-exclusive factors ("*BD* Factors") for consideration:

> (a) the similarities and material differences between the asserted art and the prior art involved during examination;
> (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
> (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;

[8] *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 (PTAB Dec. 15, 2017) (precedential as to § III.C.5, first paragraph) ("*Becton, Dickinson*").

> (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art or Patent Owner distinguishes the prior art;
> (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
> (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

Becton, Dickinson, Paper 8 at 17–18.

Advanced Bionics[9] sets out a two-part framework for analyzing these factors. In the first part, we consider factors (a), (b), and (d) to determine whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office. *Advanced Bionics*, Paper 6 at 8–10. "If, after review of factors (a), (b), and (d), it is determined that the same or substantially the same art or arguments previously were presented to the Office," we then move on to the second part of the analysis to determine "whether the petitioner has demonstrated a material error by the Office" in view of factors (c), (e), and (f). *Id.*

A. Advanced Bionics Part One

Petitioner asserts that:

> The Examiner's single rejection—considering claims differing significantly from those that ultimately issued—never considered, let alone applied, WO421, WO537, the '424 publication, NCT773 or Lovshin. Ex. 1002, 308–18. And with respect to NCT657—the only primary reference the Examiner considered—the Examiner materially misapprehended it.

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[9] *Advanced Bionics, LLC v. Med-El Electromedizinishe Geräte GmbH*, IPR2019-01469, Paper 6 at 10 (PTAB Feb. 13, 2020) (precedential) ("*Advanced Bionics*").

> WO421 and Lovshin both disclosed ranges of once-weekly doses of 0.1–1.6 mg that encompass the 1.0 mg dose now claimed. Ex. 1011; Ex. 1012. NCT773 disclosed a clinical trial using once-weekly doses of semaglutide with a maximum dose of 1.2 mg. Ex. 1014. WO537 disclosed details regarding semaglutide and specified methods of using it more broadly than NCT657. Ex. 1015. And the '424 publication disclosed formulation components not detailed in NCT657. *Compare* Ex. 1016, *with* Ex. 1013.
>
> The Examiner's single rejection of the claims concerning semaglutide focused on anticipation by NCT657 in view of post-priority date pharmacokinetic parameters. Ex. 1002, 312. The Examiner never considered WO421 or Lovshin, let alone analyzed their disclosed range of doses as related to anticipation.

Pet. 59–61.

Patent Owner responds that WO421 and WO537 were listed on an IDS and were indicated as being considered by the Examiner and WO537 is expressly discussed in the Specification of the '462 patent. Prelim. Resp. 60–61 (citing Ex. 1001, 9:43–45, 9:1–2, 21:8–9; Ex. 1002, 323). Therefore, Patent Owner asserts, these three references are "previously presented" art. *Id*. at 61.

Patent Owner further asserts that the remaining references relied upon by Petitioner in the grounds presented here are cumulative of the "previously presented" references. *Id*. For instance, Patent Owner asserts Lovshin and previously-presented WO421 are both relied on as disclosing a range of once-weekly doses 0.1 to 1.6 mg of semaglutide, and NCT773 is also relied upon for its disclosure of once-weekly administration of semaglutide in discreet doses from 0.1 mg to 1.2 mg. *Id*. Finally, Patent Owner asserts that the '424 publication, which Petitioner only relies upon for claims 4 through

10, is cumulative of WO537, which is listed on the face of the ’462 patent and is cited in its Specification. *Id*. at 61; *see also id*. at 62 (summary of how asserted references were previously presented).

Petitioner responds:

> The Office never applied any of the Petition’s prior art combinations during prosecution of the ’003[10] and ’462 patents. The Office never cited WO421, Lovshin, NCT773, WO537, or the ’424 publication. And though the Office cited a version of NCT657 as anticipating the originally filed claims of the ’462 patent, it never applied that reference to the amended claims, which limited the dose of semaglutide to 1.0 mg, despite previously recognizing that NCT657 taught doses of semaglutide up to 1.6 mg.

Reply 4.

As Patent Owner points out, whether there was a “meaningful discussion” of the asserted art during the prosecution of the ’462 patent is not the test under *Advanced Bionics* first prong; the test is “whether the art and arguments presented in the petition are the same or substantially the same as those previously presented to the Office.” *Advanced Bionics*, Paper 6 at 8–10. Here, there is no question that WO421 and WO537 were previously presented to the Office. *See* Ex. 1002, 323 (Examiner indicating both references cited in IDS were considered); Ex. 1001, code (56), 9:43–45, 21:8–9 (citing and discussing WO537). *Advanced Bionics*, Paper 6 at 7–8 (stating “[p]reviously presented art includes . . . art provided to the Office, such as on an Information Disclosure Statement (IDS)”).

[10] U.S. Patent No. 9,764,003 B2 (“the ’003 patent”) is the parent of the ’462 patent. *See* Ex. 1001, code (63).

There is also no question that a version of NCT657 was applied in a rejection of the originally filed claims of the ’462 patent, recognizing as Petitioner asserts in Ground 5 that NCT657 teaches “the use of semaglutide to treat diabetes at several different doses.” Reply 3 (citing Ex. 2001, 339–349, 398–412, 438–450); Pet. 55 (stating “NCT657 and NCT773 both disclosed semaglutide as a once-weekly treatment for type 2 diabetes in clinical trials where doses spanned between 0.1–1.6 mg in NCT657 and 0.1–1.2 mg in the later NCT 773 trial”) (citing Ex. 1003 ¶¶ 140, 145, 398; Ex. 1005 ¶¶ 277–293; Ex. 1013, 15–16; Ex. 1014, 7). Therefore, we find that NCT657 was “previously presented” to the Office.

We also agree with Patent Owner that Lovshin is cumulative of WO421 because both references are offered by Petitioner as teaching administering semaglutide at once-weekly doses between 0.1 and 1.6 mg. Pet. 6–7 (stating WO421 and Lovshin taught using semaglutide in the dose range of 0.1 to 1.6 mg to treat diabetes). Finally, we address whether the ’424 publication, asserted for dependent claims 4–10, is cumulative of WO537, and whether NCT773 is cumulative of NCT657 as asserted by Patent Owner. *See* Prelim. Resp. 61–62.

Patent Owner asserts that the ’424 publication is cumulative to WO537 without further explanation. *See* Prelim. Resp. 61. Petitioner states that challenged claims 4–10 relate to formulations of semaglutide that are “straightforward” and relies on the ’424 publication as describing formulations “as suitable for any peptide, including GLP-1 and analogues thereof.” Pet. 48. Petitioner relies on WO537 for its more specific teachings of once-weekly administration of semaglutide to treat type 2 diabetes and its

formulations. Pet. 50. Therefore, we determine that the ’424 publication is not cumulative of WO537.

We also determine that NCT773 is not cumulative of NCT657. Each of these involves different phases of clinical trials, Phase I and II, that Petitioner relies on for disclosing “semaglutide as a once-weekly treatment for type 2 diabetes in clinical trials where doses spanned between 0.1–1.6 mg in NCT657 and 0.1–1.2 mg in the later NCT773 trial.” Pet. 55 (citing Ex. 1003 ¶¶ 140, 145, 398; Ex. 1005 ¶¶ 277–293; Ex. 1013, 15–16; Ex. 1014, 7). Petitioner uses the tighter dose range in NCT773 excluding the 1.6 mg maximum does of the NCT657 trial to assert that “[t]his data point would have provided POSAs additional reason to believe a 1.0 mg once-weekly dose would be efficacious.” Pet. 57 (citing Ex. 1003 ¶¶ 404–405; Ex. 1005 ¶¶ 288–293; Ex. 1013, 16; Ex. 1014, 7). Therefore, we find that the teachings of NCT773 is not cumulative of NCT657.

Although we disagree with Patent Owner that the ’424 publication and NCT773 are cumulative of art previously presented to the Office, we find on the whole that the same art and arguments previously before the Office are now presented here, namely, a teaching that semaglutide is administered once weekly in a dose range of 0.1 to 1.6 mg that includes a dose of 1.0 mg. *See* Pet. 6–7. Therefore, we proceed to the second prong of *Advanced Bionics*.

B. Advanced Bionics Part Two

Regarding *BD* Factor (c), the Examiner rejected the original claims of the ’462 patent as anticipated by NCT647. *See* Ex. 1002, 312. The Examiner relied on the teaching in NCT647 of administration of 0.8 mg of semaglutide

once weekly as satisfying the original claim limitation requiring administration of a GLP-1 agonist to a subject in need thereof "in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week." Ex. 1002, 8–9, 312. Patent Owner responded by amending claim 1 to recite "a method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof." *Id*. at 332. The Examiner then allowed the claims stating:

> The closest prior art to the instant claims is Clinical Trial NCT00696657 ((3/25/2011) hereinafter referred to as "the '657 clinical trial"—previously cited).
>
> The '657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The semaglutide or liraglutide was used as on add-on therapy to type 2 diabetic patients already taking metformin. Efficacy of treatment was further assessed by a reduction in HbA_{1c} levels. Patients in the Arm Labels D and E of the clinical trial were administered 0.8 mg once weekly by subcutaneous injection. However, the reference does not teach or disclose a higher amount of 1 mg semaglutide.

Ex. 1002, 344–345. The Examiner did not apply any of the other references relied upon by Petitioner against the issued claims of the '462 patent.

Petitioner asserts that the Examiner erred by failing to properly consider the dose ranges for once-weekly semaglutide disclosed in WO421, Lovshin, and NCT773. Pet. 36–63. Petitioner explains concerning the teaching of both WO421 and Lovshin of "a narrow range of semaglutide from 0.1 to 1.6 mg [for the purpose of treating diabetes], which includes claim 1's 1.0 mg dose within the range," that the "Office never considered

the patentability of the issued claims in view of this disclosed range or otherwise confronted whether the disclosure of the genera in WO421 and Lovshin anticipated the issued species claims as required by MPEP 2132.02(III), or otherwise rendered the claims obvious. Patentability in view of this range is therefore a legal theory raised in the Petition that the Office never addressed." Reply 4–5; Pet. 62.

Petitioner also asserts that the Examiner's Reason for Allowance finding NCT657 teaches 0.8 mg semaglutide in Arm Labels D and E, but does not "teach or disclose a higher amount of 1 mg semaglutide" is incorrect. Petitioner states:

> The Examiner failed to recognize experimental arm F in NCT657 administered patients 1.6 mg semaglutide once weekly. *Compare* Ex. 100-2, 344–45, *with* Ex. 1013, 16. It was therefore wrong for the Examiner to conclude NCT 657 did not disclose administration of any dose of semaglutide higher than 0.8 mg. *Compare* Ex. 1002, 344–45, *with* Ex. 1013, 15–16. The Examiner's obvious error in failing to consider the full scope of the reference, e.g., failing to recognize the administration of a dose higher than the claimed dose at the time, was material to patentability because the Examiner issued the patent on the understanding "a" higher amount was not disclosed.

Pet. 64 (citations omitted).

Patent Owner points to rejections the Examiner made in the parent application applying NCT657 "including both obviousness and anticipation rejections in which NCT 657's 1.6 mg dose was expressly discussed." Prelim. Resp. 64–65.

We find that Petitioner has demonstrated material error by the Office. The Examiner's statement that NCT657 "does not teach or disclose a higher amount of 1 mg semaglutide" is incorrect and also fails to consider the

teachings of the dosing ranges of WO421 and Lovshin, and the maximum dose of 1.2 mg of semaglutide taught in NCT773.

For these reasons, we determine that Petitioner has sufficiently demonstrated a material error on the part of the Examiner, and we therefore decline to exercise our discretion to deny institution of *inter partes* review under 35 U.S.C. § 325(d).

IV. DISCRETION UNDER 35 U.S.C. § 314(a)

Patent Owner asserts that we should use our discretion to deny the Petition under Section 314(a), "particularly in light of the significant §325(d) concerns regarding Grounds 1 and 2—which address only claims 1–3—and in view of the substantive infirmities of Ground 3–5." Prelim. Resp. 66–67. Patent Owner does not address Petitioner's assertions that a trial here would most likely conclude before the parallel Delaware litigation, and Petitioner's stipulation "that if the Board institutes, Petitioner will not pursue in the district court any instituted grounds against the originally-issued claims unless a change in law otherwise permits." Pet. 65–66 (citing *Sand Revolution II, LLC v. Cont'l Intermodal Grp*., IPR2019-01393, Paper 24, 12 (PTAB June 16, 2020)).

We do not agree with Patent Owner's assertions concerning Section 325(d) as set forth above, and find nothing here that would warrant the exercise of our discretion to deny institution based on 35 U.S.C. § 314(a) to deny institution of an otherwise meritorious petition.

V. ANALYSIS OF THE ASSERTED GROUNDS

A. Legal Standards

"In an [*inter partes* review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable." *Harmonic Inc. v. Avid Tech., Inc*., 815 F.3d 1356, 1363 (Fed. Cir. 2016) (citing 35 U.S.C. § 312(a)(3) (requiring *inter partes* review petitions to identify "with particularity . . . the evidence that supports the grounds for the challenge to each claim")). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat'l Graphics, Inc*., 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review).

To show anticipation under § 102, each and every claim element, arranged as in the claim, must be found in a single prior art reference. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359 (Fed. Cir. 2008). The prior art need not, however, use the same words as the claims in order to find anticipation. *In re Gleave*, 560 F.3d 1331, 1334 (Fed. Cir. 2009). It is also permissible to take into account not only the literal teachings of the prior art reference, but also the inferences an ordinarily skilled person would draw from the reference. *Eli Lilly and Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr*., 849 F.3d 1073, 1074–75 (Fed. Cir. 2017); *In re Preda*, 401 F.2d 825, 826 (CCPA 1968). A reference may also anticipate a claim even if it does not expressly teach all the limitations arranged or combined as in the claim, "if a person of skill in the art, reading the reference, would 'at once envisage' the claimed arrangement or combination." *Microsoft Corp. v. Biscotti, Inc.*, 878 F.3d 1052, 1068 (Fed.

Cir. 2017) (quoting *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015)).

A claim is unpatentable under 35 U.S.C. § 103 if the differences between the claimed invention and the prior art are such that the claimed invention as a whole would have been obvious before the effective filing date of the claimed invention to a person having ordinary skill in the art to which the claimed invention pertains. *See KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved on the basis of underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) objective evidence of nonobviousness, if any. *Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

In analyzing the obviousness of a combination of prior art elements, it can be important to identify a reason that would have prompted one of skill in the art "to combine . . . known elements in the fashion claimed by the patent at issue." *KSR*, 550 U.S. at 418. A precise teaching directed to the specific subject matter of a challenged claim is not necessary to establish obviousness. *Id.* Rather, "any need or problem known in the field of endeavor at the time of invention and addressed by the patent can provide a reason for combining the elements in the manner claimed." *Id.* at 420.

Accordingly, a party that petitions the Board for a determination of unpatentability based on obviousness must show that "a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan

would have had a reasonable expectation of success in doing so." *In re Magnum Oil Tools Int'l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016) (internal quotation marks omitted). "Both the suggestion and the expectation of success must be founded in the prior art, not in the applicant's disclosure." *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988).

An obviousness analysis "need not seek out precise teachings directed to the specific subject matter of the challenged claim, for a court can take account of the inferences and creative steps that a person of ordinary skill in the art would employ." *KSR*, 550 U.S. at 418; *see In re Translogic Tech, Inc.*, 504 F.3d 1249, 1259 (Fed. Cir. 2007). In *KSR*, the Supreme Court also stated that an invention may be found obvious if trying a course of conduct would have been obvious to a POSITA:

> When 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. If this leads to the anticipated success, it is likely the product not of innovation but of ordinary skill and common sense. In that instance the fact that a combination was obvious to try might show that it was obvious under § 103.

550 U.S. at 421. "*KSR* affirmed the logical inverse of this statement by stating that § 103 bars patentability unless 'the improvement is more than the predictable use of prior art elements according to their established functions.'" *In re Kubin*, 561 F.3d 1351, 1359–60 (Fed. Cir. 2009) (citing *KSR*, 550 U.S. at 417).

We analyze the asserted grounds of unpatentability in accordance with the above-stated principles. In making such an analysis, we find that

Petitioner has shown a reasonable likelihood of prevailing in establishing that at least claim 1 of the ’462 patent is unpatentable.

B. Level of Ordinary Skill in the Art

In determining the level of skill in the art, we consider the type of problems encountered in the art, the prior art solutions to those problems, the rapidity with which innovations are made, the sophistication of the technology, and the educational level of active workers in the field. *See Custom Accessories, Inc. v. Jeffrey-Allan Industries, Inc.*, 807 F.2d 955, 962 (Fed. Cir. 1986); *see also Orthopedic Equip. Co. v. United States*, 702 F.2d 1005, 1011 (Fed. Cir. 1983).

In addressing the level of ordinary skill in the art, Petitioner contends a person of ordinary skill in the art ("POSA") would have

> (1) an M.D., Pharm.D., or Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

Pet. 8–9; *see* Ex. 1003 ¶¶ 26–28; Ex. 1005 ¶¶ 29–31; Ex. 1007 ¶¶ 25–27.[11] Patent Owner does not offer a different level of ordinary skill in the art at this stage of the proceeding. *See generally* Prelim. Resp.

On the current record, and for the purposes of this decision, we accept Petitioner’s proposed definition, as it appears consistent with the level of

[11] We need not consider Petitioner’s similar alternative definition. *See* Pet. 9.

skill in the art reflected in the prior art of record and the disclosure of the ’462 Patent. *See Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001) (“the prior art itself [may] reflect[] an appropriate level” as evidence of the ordinary level of skill in the art (quoting *Litton Indus. Prods., Inc. v. Solid State Sys. Corp.*, 755 F.2d 158, 163 (Fed. Cir. 1985)).

C. Claim Construction

We interpret a claim “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).” 37 C.F.R. § 42.100(b) (2020). Under this standard, we construe 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.” *Id.* Moreover, “the specification ‘is always highly relevant to the claim construction analysis. Usually it is dispositive; it is the single best guide to the meaning of a disputed term.’” *In re Abbott Diabetes Care Inc.*, 696 F.3d 1142, 1149 (Fed. Cir. 2012) (quoting *Phillips v. AWH Corp.*, 415 F.3d 1303, 1315 (Fed. Cir. 2005) (en banc)).

Petitioner asserts that no claim term needs to be construed and all terms should be accorded their plain and ordinary meaning. Pet. 14. Petitioner, however, addresses the preamble of claim 1—“a method for treating type 2 diabetes.” Petitioner cites to the Specification of the ’462 patent that expressly describes the terms “treatment” and “treating” in concluding that “[n]othing in the specification or prosecution history suggests that the phrase requires any degree of efficacy, e.g., a particular level of reduction in HbA_{1c}.” *Id.* at 14–15. Petitioner concludes that the plain and ordinary meaning of the preamble “would be understood by POSAs to

broadly encompass administering semaglutide to alleviate or reduce symptoms and complications associated with type 2 diabetes or otherwise manage the disease," with no requirement for any particular treatment effect. *Id*. at 15.

Patent Owner agrees that the preamble of claim 1 is limiting and asserts the preamble means "the claimed administration is for the care or management of a patient with type 2 diabetes." Prelim. Resp. 13.

In construing a claim term, we start with the language of the claims themselves. *See Phillips*, 415 F.3d at 1314 (stating "the claims themselves provide substantial guidance as to the meaning of particular claim terms"). A preamble to a claim should be construed as limiting the scope of the claim "[i]f the claim preamble, when read in the context of the entire claim, recites limitations of the claim, or, if the claim preamble is 'necessary to give life, meaning, and vitality' to the claim." *Pitney Bowes, Inc. v. Hewlett-Packard Co*. 182 F.3d 1298, 1305 (Fed. Cir. 1999). The Federal Circuit has also stated:

> [D]ependence on a particular disputed preamble phrase for antecedent basis may limit claim scope because it indicates a reliance on both the preamble and claim body to define the claimed invention. Likewise, then the preamble is essential to understand limitations or terms in the claim body, the preamble limits claim scope.

Catalina Marketing Int'l v. Coolsavings.com, Inc., 289 F.3d 801, 808 (Fed. Cir. 2002) (citing *Bell Communications Res., Inc. v. Vitalink Communications Corp*., 55 F.3d 615, 620 (Fed. Cir. 1995); *Pitney Bowes*, 182 F.3d at 1306).

Here, we agree with the parties that the preamble of claim 1 is limiting. The preamble provides context for the requirement of claim 1 that administration of the semaglutide is "to a subject in need thereof." *See* Ex. 1001, 35:42–44. The preamble, when read in the context of the entirety of claim 1, recites a limitation of administering semaglutide to a subject with type 2 diabetes.

Based on the constructions of the preamble provided by the parties, it appears they agree that the preamble does not require any particular level of efficacy. We agree. The Specification of the '462 patent makes clear that "treatment" or "treating" as used in the '462 patent does not require any particular degree of efficacy as these terms include the "full spectrum" of treatments for a condition. *See* Ex. 1001, 5. For instance, the Specification of the '462 patent provides:

> In one embodiment the term "treatment" or "treating" as used herein means the management and care of a patient for the purpose of combating a condition, such as a disease or a disorder. In one embodiment the term "treatment" or "treating" is intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition.

Ex. 1001, 5:16–27.

Having considered the record, we determine that no further express claim construction of any claim term is necessary to reach our decision. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) ("The

Board is required to construe 'only those terms that . . . are in controversy, and only to the extent necessary to resolve the controversy.'") (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)); *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co. Ltd. v. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017) ("[W]e need only construe terms 'that are in controversy, and only to the extent necessary to resolve the controversy.'" (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999))).

D. *References Relied Upon for the Anticipation Grounds*

Petitioner asserts that claims 1 through 3 of the '426 are anticipated by both WO421 and Lovshin. Pet. 4, 26–28.

i. WO421 (Ex. 1011)

WO421 describes methods for treating or preventing metabolic diseases, such as type 2 diabetes mellitus, comprising the combined administration of a GLP-1 receptor agonist and a certain DPP-4 inhibitor. Ex. 1011, 2:4–7; 11:34–12:4. WO421 describes DPP-4 inhibitors and GLP-1 as follows.

> The enzyme DPP-4 (dipeptidyl peptidase IV) also known as CD26 is a serine protease known to lead to the cleavage of a dipeptide from the N-terminal end of a number of proteins having at their N-terminal end a proline or alanine residue. Due to this property DPP-4 inhibitors interfere with the plasma level of bioactive peptides including the peptide GLP-1 and are considered to be promising drugs for the treatment of diabetes mellitus.
>
> * * *

> Glucogon-like peptide-1 (GLP-1) is a hormon[e] secreted from enterendocrine L cells of the intestine in response to food. Exogenous GLP-1 administration at pharmacological doses results in effects that are beneficial for treating type 2 diabetes. However, native GLP-1 is subject to rapid enzymatic degradation. The action of GLP-1 is mediated through the GLP-1 receptor (GLP-1R).

Ex. 1011, 6:23–7:5. WO421 lists semaglutide as a preferred example of a GLP-1 receptor agonist. Ex. 1011, 33:20–23.

WO421 states that "the combinations composition or combined uses according to this invention may envisage the simultaneous, sequential or separate administration of the active components or ingredients." Ex. 1011, 35:9–11. In further describing the combination therapy, WO421 states:

> The combined administration of this invention may take place by administering the active components or ingredients together, such as e.g. by administering them simultaneously in one single or in two separate formulations or dosage forms. Alternatively, the administration may take place by administering the active components or ingredients sequentially, such as e.g. successively in two separate formulations or dosage forms.
>
> For the combination therapy of this invention the active components or ingredients may be administered separately (which implies that they are formulated separately) or formulated altogether (which implies that they are formulated in the same preparation or in the same dosage form). Hence, the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination. Preferably, for the combination therapy according to this invention the DPP-4 inhibitor and the GLP-1 receptor agonist are administered in different formulations.

> Unless otherwise noted, combination therapy may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.

Ex. 1011, 37:7–23.

In discussing dosages, WO421 states that "[t]he GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art." Ex. 1011, 43:1–3. WO421 specifically states that: "Semaglutide is administered once weekly by subcutaneous injection (0.1–1.6 mg)." *Id*. at 43:13.

ii. Lovshin (Ex. 1012)

Lovshin is a review of the data from clinical trials assessing GLP-1R agonists and DPP-4 inhibitors reflected, which Lovshin asserts "are now routinely used to treat type 2 diabetes mellitus." Ex. 1012, Abstr., 262–263. Table 1 of Lovshin is set forth below summarizes the incretin-based therapies in clinical trials that Lovshin reviews.

Table 1 | Incretin-based therapies

Agent	Dose	Status
GLP-1R agonists (subcutaneous injection)		
Exenatide	5–10 μg twice daily	A
Liraglutide	1.2–1.8 mg once daily	F
AVA0010	5–30 μg once or twice daily	I
Exenatide QW	2 mg once weekly	I
Taspoglutide	20–30 mg once weekly	I
Albiglutide	30–50 mg once weekly	I
CJC-1134-PC	1.5–3 mg once or twice weekly	I
NN9535	0.1–1.6 mg once weekly	I
LY2189265	0.25–3 mg once weekly	I
LY2428757	0.5–17.6 mg once weekly	I
DPP-4 inhibitors (oral)		
Sitagliptin	25–100 mg once daily	A
Vildagliptin	50 mg twice daily	A
Alogliptin	12.5–25 mg once daily	F
Saxagliptin	5–10 mg once daily	F
Linagliptin	2.5–5 mg once daily	I
Dutogliptin	200–400 mg once daily	I

Abbreviations: QW, once weekly; A, approved; F, filed for regulatory approval; I, being investigated.

Table 1 set forth above shows NN9635, which Petitioner asserts is semaglutide, is being investigated in a dosage range from 0.1 to 1.6 mg once weekly. Ex. 1012, 263; Pet. 37. Lovshin also states that multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I–II studies, including NN9635, "but few data are available on the structure or efficacy of these molecules." *Id*. at 266. Lovshin concludes:

> Although the use of incretin-based drugs is still expensive and experience with these agents is limited, the development of multiple new agents will broaden the interest in and feasibility of incretin-based therapies for T2DM [Type 2 diabetes mellitus]. Although these agents offer several important advantages over commonly used drugs, including a glucose-dependent mechanism of action and no risk of weight gain, much information remains to be learned about their long-term

> efficacy, safety, and durability of effect. Hence, physicians should approach incretin-based agents with a mixture of cautious enthusiasm and critical scrutiny, to ensure that these drugs meet the demands that are expected for agents used to treat a chronic and complex disease.

Ex. 1012, 268.

E. Grounds 1 and 2: Anticipation of Claim 1 through 3 by each of WO421 and Lovshin

Petitioner contends claims 1 through 3 are anticipated by each of WO421 and Lovshin. *See* Pet. 26–42. Petitioner presents evidence and argument to show that each of the limitations of these claims is taught by each of WO421 and Lovshin *Id.*

Beginning with independent claim 1, we determine that Petitioner has met its burden for institution. Based on the current record, Petitioner has shown that WO421 and Lovshin each teaches all of the limitations of the recited combination.

For instance, Petitioner points to where both WO421 and Lovshin expressly disclose "a method for treating type 2 diabetes." *See* Pet. 26–27 (citing Ex. 1003 ¶¶ 233–234; Ex. 1005 ¶¶ 180–183; Ex. 1011, 2:4–5, 62:24–29 (claim 17)); Pet. 36–37 (citing Ex. 1012, 1). Petitioner also shows sufficiently for institution where WO421 and Lovshin teach such treatment "comprising administering semaglutide." *See* Pet. 27–29 (citing, e.g., Ex. 1011, 34:20–22, 65:26–31 (claim 17)); Pet. 36–37 (identifying Lovshin as teaching investigation of treatment with "NN9535" also known as semaglutide). Although WO421 relates to a combination therapy of a GLP-1 receptor agonist and a DPP-4 inhibitor, we agree with Petitioner on the record before us that the transitional term "comprising" in claim 1 "allows

for administration of additional therapeutics along with semaglutide." Pet. 29 (citing *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003)).[12] Petitioner points to Lovshin's teaching

We also find that Petitioner has shown sufficiently that both WO421 and Lovshin teach administration of semaglutide "once weekly in an amount of 1.0 mg." Pet. 29–35, 37. Specifically, Petitioner points to the statement in WO421 that "semaglutide is administered once weekly by subcutaneous injection (0.1 to 1.6 mg)," and a similar statement in Lovshin. *Id*. at 29–30 (citing Ex. 1011, 44:14); *id*. at 37 (citing Ex. 1012, 2 (Table 1)). Petitioner asserts that this disclosed narrow range of once-weekly doses in WO421 and Lovshin anticipate the '462 patent's claim to a 1.0 mg once-weekly dose because "POSAs would understand the 0.1–1.6 mg dose range in WO421 [and Lovshin] to be a disclosure of a discrete and limited claims of doses a POSA can at once envisage." *Id*. at 30.

Petitioner explains how the genus of the narrow 0.1 to 1.6 mg dose range for semaglutide anticipates the species 1.0 mg dose as follows. *See* Pet. 30.

> The prior art range—0.1 to 1.6 mg—is a disclosure of a discrete number of doses. POSAs would view that range of

[12] Petitioner also relies on statements in WO421 stating that semaglutide and DPP-4 inhibitors may be administered "simultaneously, *separately*, sequentially or chronologically" would indicate to a POSA that this would include administration of semaglutide alone, including in a separate course of treatment. Pet. 27–28 (citing Ex. 1011, 37:2–24); Ex. 1003 ¶¶ 235–247; Ex. 1005 ¶¶ 184–188). Because we agree that the claims encompass combination therapy of semaglutide and DPP-4 inhibitors, we need not address this argument in detail although it appears meritorious on the record before us.

> doses as encompassing *at most* 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5 and 1.6 mg—a group of just 16 doses. Prior art clinical trials for semaglutide adjusted doses in increments no less than 0.1 mg/dose. For example, 0.1 mg is the smallest dose administered to NCT657, which administered doses that doubled—e.g. 0.1, 0.2, 0.4, 0.8 and 1.6 mg. The prior art adjusted semaglutide doses in a minimum of 0.1 mg increments and offered no reason to believe any more precise dose was necessary.

Pet. 31 (citing Ex. 1003 ¶¶ 256–260; Ex. 1005 ¶¶ 189–192; Ex. 1013, 7–8, 15–16). Petitioner also relies on the dosing increments of liraglutide of 0.6 mg increments to reinforce its position that "POSAs would not expect dose adjustments smaller than 0.1 mg to be meaningful for semaglutide." Pet. 31–32.

Finally, Petitioner asserts that there is nothing to suggest that a 1.0 mg dose is critical, and a POSA would understand from the clinical trials of semaglutide that "there was a reasonable basis to believe semaglutide would have a treatment effect across the entire dose range" of 0.1 to 1.6. Pet. 32 (citing Ex. 1005 ¶ 190). Petitioner concludes, "[t]he lack of any criticality of the 1.0 mg dose reinforces that POSAs would immediately envisage a once-weekly 1.0 mg dose from the prior art." Pet. 32.

On this record, we find Petitioner's argument persuasive that the narrow once-weekly dosing range of 0.1 to 1.6 for semaglutide would anticipate a 1.0 mg, once-weekly dose because the range provides a relatively finite number of doses, including 1.0 mg, and the evidence suggests that all of these doses would provide treatment for type 2 diabetes as defined by the '462 patent. We also agree that the record evidence does not support an assertion that the 1.0 mg dose is critical.

Whether a generic disclosure necessarily anticipates everything within the genus depends on the factual aspects of the specific disclosure and the particular products at issue. *Sanofi-Synthelabo v. Apotex, Inc*., 550 F.3d 1075, 1083 (Fed. Cir. 2008). WO421 and Lovshin can each anticipate claim 1 if the references each describe the limitations of claim 1, but "'[d]oes not expressly spell out' the limitations as arranged or combined as in the claim, if a person of skill in the art reading the reference, would 'at once envisage' the claimed arrangement or combination." *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015) (quoting *In re Petering*, 301 F.2d 676, 681 (CCPA 1962)). In applying this concept in *In re Petering*, the CCPA found a reference anticipated a claimed compound where a generic chemical formula with preferred substituents defined a more limited generic class of about 20 compounds, anticipated the claimed compound that was one of the 20. *In re Petering*, 301 F.2d at 682; *see also Eli Lilly & Co. v. Zenith Goldline Pharma. Inc.*, 471 F.3d 1369, 1376 (Fed. Cir. 2006) (characterizing *Petering* as "expressly spell[ing] out a definite and limited class of compounds that enabled a person of ordinary skill in the art to at once envisage each member of this limited class").

Here, WO421 and Lovshin teach a relatively narrow range for a weekly dose of semaglutide, 0.1 to 1.6 mg, and a POSA would be informed from the dosing scheme in NCT657 administering doses that doubled from 0.1 mg to 1.6 mg with the smallest increase of 0.1 mg, that a finite number of practical choices in the range exist with 1.0 mg being one of those choices. This appears especially true when no record evidence currently

exists that any part of the range from 0.1 to 1.6 mg of semaglutide could not be used to treat type 2 diabetes or that the 1.0 mg dose is critical.

Finally, both WO421 and Lovshin teach administering semaglutide "to a subject in need thereof." Pet. 34–35 (citing Ex. 1011, 8:35–10:7 (describing eligible patients for treatment)); Pet. 36–37 (Lovshin).

Patent Owner makes several arguments as to why WO421 and Lovshin do not anticipate claims 1 through 3 of the '462 patent, which we do not find persuasive on the record before us. First, Patent Owner asserts that the genus of 0.1 to 1.6 mg for a weekly dose of semaglutide is too broad, spanning from 10% to 160% of the claimed 1.0 mg dose. Prelim. Resp. 14–15, 31. Patent Owner points to other disclosures in WO421 and Lovshin reciting substantially smaller doses of other GLP-1 antagonists, such as exenatide or lixisenatide. *Id*. Based on these doses, Patent Owner asserts "[n]either Petitioner nor its experts address whether a POSITA would 'at once envisage' the claimed 1.0 mg dose if the dose adjustment increment were as small of 0.005 milligrams—which would yield at least *320* possible doses in WO421'S 0.1 mg–1.6 mg range—As Petitioner's cases require." Prelim. Resp. 15–16 (citing Pet. 30 (citing *In re Petering*, 301 F.2d 676, 682 (CCPA 1962))), 31.

We are not persuaded by Patent Owner's argument. It is not clear why a POSA would look to the dosing for exenatide or lixisenatide versus the dosing of the claimed semaglutide in clinical trials to inform the possible choices for dosing from the 0.1 to 1.6 mg range. As we have set forth above,

we find that a POSA would look to the dosing of semaglutide in clinical trials.[13]

Patent Owner also disagrees that the 1.0 mg dose of semaglutide is not critical. Prelim. Resp. 19–23, 31. Patent Owner points to the statement in the '462 patent that "the methods of the present invention provide[] ***surprisingly . . . improved*** reduction of HbA1c" (Ex. 1001, 2:56–58 (emphasis in original)), "and repeatedly discloses that only once-weekly doses of ***0.8 mg or greater*** showed improvements over once-daily liraglutide . . . ." Prelim. Resp. 19. As we have determined as set forth above, claim 1 of the '462 patent does not require any particular level of efficacy, and certainly not as compared to the efficacy of a particular once-daily liraglutide dose. *See supra* Section V.C.

Patent Owner also asserts that Petitioner's anticipation challenge inappropriately relies on multiple embodiments in WO421 and Lovshin. Prelim. Resp. 23–26, 31–32. Patent Owner states "Petitioner fails to show how the isolated disclosure of a broad range of semaglutide doses . . . is a disclosure of using such doses to *treat* type 2 diabetes." *Id*. at 24, 31–32. We disagree. Both WO421 and Lovshin link GLP-1 receptor agonists, such as semaglutide, to the treatment of type 2 diabetes mellitus. *See* Ex. 1011, 2:1–9, 33:20–23, 43:1–3, 13; Ex. 1012, Abstr., 263 (Table 1), 266 (long-acting

[13] Patent Owner also cites *Mylan Pharms. Inc. v. Boehringer Ingelheim Int'l GmbH* to support its position. In *Mylan*, however, the prior art range genus was much broader than in this case. *See* IPR2016-01566, Paper 15 at 7–9 (disclosed ranges were "1 to 100 mg, preferably 1 to 100 mg, in each case 1 to 4 times therein a day," to the claimed doses of 2.5 and 5 mg, and Petitioner did not argue a POSA would understand any dose withing the preferred range administered 1 to 4 times a day would be efficacious).

GLP-1R agonists include NN9535 (semaglutide)). This does not constitute inappropriate picking and choosing among disparate embodiments. Patent Owner also asserts that Petitioner fails to show that WO421 or Lovshin teach treating type 2 diabetes with semaglutide, which is similar to its inappropriate picking and choosing argument, and equally unavailing on the record before us here. Prelim. Resp. 26–27, 33–34.

Lastly, Patent Owner asserts that neither WO421 nor Lovshin are enabled for "a method of treating" type 2 diabetes. Prelim. Resp. 27–29, 35. Patent Owner states "WO421's mere disclosure of a broad range of possible doses fails to enable use of semaglutide to *treat* any of the dozens of diseases identified therein, let alone type 2 diabetes with 1.0 mg semaglutide, whether in combination or alone." Prelim. Resp. 28. Patent Owner also states that "Lovshin simply confirms PO was undertaking the laborious experimentation required to determine whether semaglutide could be safely administered, and, if so, whether and which semaglutide dosage *might* be effective and for what conditions." *Id*. at 35.

Petitioner asserts that nothing more is required from either WO421 or Lovshin for enablement than the teaching in each that "semaglutide would be given to diabetic patients at a once-weekly dose between 0.1 and 1.6 mg, which included 1.0 mg." Pet. 36, 38. We agree. If WO421 and Lovshin each describe the claimed invention in sufficient detail to enable a POSA to carry out the claimed invention, "proof of efficacy is not a required for a prior art reference to be enabling for purposes of anticipation." *See Impax Labs. Inc. v. Aventis Pharm. Inc.*, 468 F.3d 1366, 1383 (Fed. Cir. 2006). Here, we find on the record before us that both WO421 and Lovshin each describe the

method of treating type 2 diabetes as set forth in claim 1 of the ’462 patent, i.e., administering 1 mg once-weekly of semaglutide to a diabetic patient for the purpose of combatting diabetes, such that a POSA would carry out the invention of claim 1. *See* Ex. 1003 ¶¶ 130–137, 231–269; Ex. 1005 ¶¶ 180–195.

Accordingly, based on the current record, Petitioner has established a reasonable likelihood it will prevail in demonstrating that at least claims 1 is anticipated by each of WO421 and Lovshin.

F. Grounds 3–5: Obviousness Grounds

Petitioner contends claims 1–10 would have been obvious over WO421 and the ’421 Publication, *see* Pet. 44–50, over WO537 and Lovshin, *see* Pet. 50–54, and over NCT657, NCT733, and the ’424 publication, *see* Pet. 54–59. Petitioner asserts that even if neither WO421 nor Lovshin anticipates claim 1 because of the difference in the dose range 0.1 to 1.6 mg versus the 1.0 mg dose of claim 1, claim 1 would have been obvious because “selecting a 1.0 mg dose is merely a routine, non-patentable optimization of a result-effective variable disclosed within that narrow and finite prior art range.” Pet. 44 (citing Ex. 1003 ¶¶ 323–328; Ex. 1005 ¶¶ 227–238; e.g., *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367–68 (Fed. Cir. 2007)).

As Dr. Bantle testifies, a POSA would have known the once-weekly dosing for semaglutide along with its longer half-life would satisfy a patient’s desire for fewer injections and less side effects. Ex. 1003 ¶ 323. Therefore, in Dr. Bantle’s opinion, semaglutide, already known in the prior art, was an obvious choice for optimization with a significant amount of information in the prior art concerning semaglutide, including the clinical

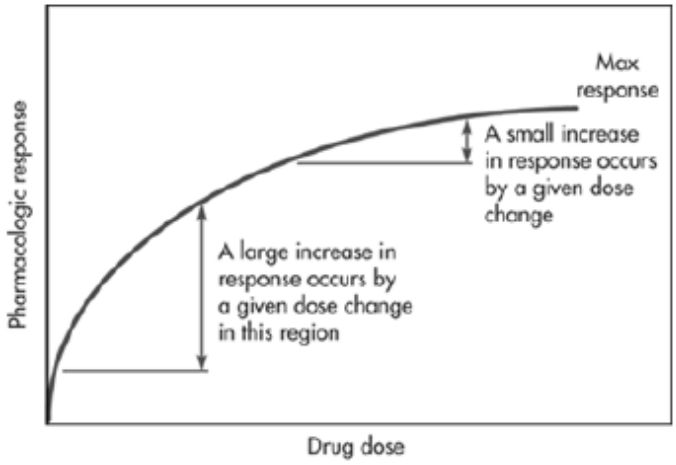
trials, to direct a POSA to the right dose in the narrow range in the prior art. *Id*. As Petitioner points out "POSAs had to optimize only a single variable—dose size—from only 16 reasonably possible prior art options and with significant guidance pointing directly to 1.0 mg. Thus, the 1.0 mg once-weekly dose was, at least, obvious to try." Pet. 47 (citing Ex. 1001 ¶ 327; Ex. 1005 ¶ 233), 40.

Petitioner also asserts that a POSA would have a reasonable expectation of success in choosing the 1.0 mg once-weekly dose of semaglutide. Pet. 40–44. Both WO421 and Lovshin taught the once-weekly range of 0.1 to 1.6 mg of semaglutide and the two clinical trials, NCT657 and NCT773 taught weekly dose ranges of 0.1 to 1.6 mg and 0.1 to 1.2 mg, respectively. Pet. 40 (citing Ex. 1003 ¶¶ 98–102, 130–137, 256, 259, 298, 401; Ex. 1005 ¶¶ 225, 227–236; Ex. 1011, 44:13; Ex. 1012, 2; Ex. 1013, 15–16; Ex. 1014, 7). Both Drs. Bantle and Jusko testify that a POSA would have been motivated to optimize the dose within the known range because it is a result effective variable. Pet. 41 (citing Ex. 1003 ¶¶ 396–407; Ex. 1005 ¶¶ 223–239). Petitioner relies on Dr. Jusko's testimony concerning how the clinical trials are generally conducted to bolster this conclusion.

Dr. Jusko testifies as to drug development and clinical trial design to explain the approval process for a new drug. Ex. 1005 ¶¶ 65–74. Dr. Jusko explains that:

> As the dose of the drug increases, the concentration at the receptor or target site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum pharmacologic effect (E_{max}) at the plateau on the dose-response curve, as

> shown in the figure below (reproduced from Figure 19-1 of Shargel). *Id.* at 81–82.



> Typically, the optimal dose is often the smallest dose providing the near maximal treatment effect (i.e., the lowest dose near or on the plateau) because higher doses usually result in higher adverse event rates. To best understand the Exposure/Response of a drug, phase II studies typically investigate a range of doses including lower doses and higher doses that are predicted to be on the dose-response curve plateau. *See* Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1–2, 4, 6.

Ex. 1005 ¶¶ 70–71.

Both Lovshin and NCT657 disclose a Phase II study of semaglutide, the purpose of which is to determine the dose-response curve in humans. Pet. 43 (citing Ex. 1003 ¶ 399; Ex. 1005 ¶¶ 65–74. Therefore, a POSA "would have understood the doses at the upper end of the dosing range would be expected to treat type 2 diabetes." Pet. 43 (citing Ex. 1003 ¶¶ 325–330; Ex. 1005 ¶¶ 65–74, 227–238). Petitioner also points to the later NCT773 study for a narrower dose range from 0.1 to 1.2 mg as further

supporting the reasonable expectation of success in choosing a 1.0 mg dose. Pet. 43–44.

"Discovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art." *In re Boesch*, 617 F.2d 272, 276 (CCPA 1980). We agree with Petitioner on the record before us that determining the 1.0 mg once-weekly dose for semaglutide as set forth in claim 1 in light of the information in the prior art including the dose ranges and specific doses used in the clinical trials would require routine optimization of a result effective variable, the dose for semaglutide. We credit the testimony of Drs. Bantle and Jusko described above as providing reasons for why a POSA would be motivated to determine the 1.0 mg dose and have a reasonable expectation of success in doing so.

Patent Owner asserts that there is no safety or efficacy data in the record upon which Petitioner can base a POSAs motivation to select a 1.0 mg dose, much less with a reasonable expectation of success, especially when neither clinical study, NCT657 nor NCT773, tested the 1.0 mg dose. Prelim. Resp. 36–45. Patent Owner also points to a statement in the '462 patent that describes once-weekly semaglutide "*surprisingly* showed improved reduction of HbA1c" as compared to liraglutide administered once daily at higher doses. *Id*. at 58 (citing Ex. 1001, 2:56–58). On balance on the record before us, we do not find Patent Owner's arguments persuasive. Although Petitioner can point to no prior art safety and efficacy data for the 1.0 mg dose in the record, we agree that the progression in testing once-weekly doses of semaglutide in a narrow range that contains the 1.0 mg dose to Phase II clinical trials would indicate to a POSA at least some efficacy in

treating a patient with type 2 diabetes, and would motivate a POSA to optimize the dose with a reasonable expectation of success. *See, e.g.*, Ex. 1012, 263. We also note that the bald statement of "surprising" results without more does not convince us that any secondary indicia would indicate non-obviousness. Also, we again note that no particular level of efficacy is required by the claims.

Accordingly, based on the current record, Petitioner has established a reasonable likelihood it will prevail in demonstrating that at least independent claim 1 would have been obvious based on the obviousness Grounds 3 through 5 set forth in the Petition.

VI. CONCLUSION

Based on the current record, we determine Petitioner has shown a reasonable likelihood that it will prevail in establishing that at least one claim of the '462 patent is unpatentable. Accordingly, we institute review of all claims challenged on all of the grounds in the Petition. *See* Patent Trial and Appeal Board Consolidated Trial Practice Guide (Nov. 2019), 64, *available at* https://www.uspto.gov/ sites/default/files/documents/tpgnov.pdf.

At this stage of the proceeding, the Board has not made a final determination as to the patentability of any challenged claim. Our view with regard to any conclusion reached in the foregoing analysis could change upon completion of the record.

VII. ORDER

Accordingly, it is:

ORDERED that pursuant to 35 U.S.C. § 314, an *inter partes* review is hereby instituted as to claims 1–10 of the ’462 patent based on the unpatentability challenges presented in the Petition; and

FURTHER ORDERED that pursuant to 35 U.S.C. § 314(c) and 37 C.F.R. § 42.4, notice is hereby given of the institution of a trial commencing on the entry date of this decision.

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