

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., DR. REDDY'S LABORATORIES, INC.,
and DR. REDDY'S LABORATORIES, LTD.

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00724¹

Patent No. 10,335,462

PETITIONER'S REPLY

¹ IPR2024-00009 (Dr. Reddy's Laboratories) has been joined with this proceeding.

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I. Introduction

Patent Owner (PO) cannot avoid Petitioner's grounds with defenses that fall short upon cursory review. Its inventor attempts to antedate references by asserting earlier conception, but she admitted others came up with the idea of a 1.0mg semaglutide dose. Its technical expert asserts skilled artisans (POSAs) wouldn't envisage 1.0mg from the known 0.1-1.6mg range because there were too many other doses in that range, but he admitted not considering the scope of "1.0" with its single significant figure. PO's secondary considerations experts assert commercial success without knowledge of other Novo patents or consideration of whether Ozempic®'s success came from the known semaglutide molecule; they assert unexpected results without considering the closest prior art or whether the results were merely a difference in degree; they assert long-felt need without addressing other known safe and effective once-weekly GLP-1 T2D treatments; and they assert industry praise based on Novo's own articles and mainstream media stories unconnected to the claims.

Nor can PO avoid unpatentability with arguments ignoring or miscasting Petitioner's evidence and governing precedent. The Board should find the challenged claims unpatentable for the reasons described in the Petition and below.

II. Dr. Jensen's declaration is insufficient and lacks corroboration

PO cannot antedate WO421 and portions² of NCT773 because neither Jensen's declaration nor any corroborating evidence establish that she conceived a T2D treatment with a once-weekly 1.0mg semaglutide dose before 2012.³ POR. 13-19, 73-74.

A. Novo's development of the 1.0mg dosing regimen

When Jensen joined Novo in 2007, its Phase I semaglutide study [REDACTED] [REDACTED]. Ex1312 (Jensen Dep.) (12:3-14). Her work involved designing the Phase 2 trial, NN9535-1821 ("1821 trial"), which tested once-weekly semaglutide doses for T2D treatment, but not a 1.0mg dose. *Id.* (19:1-4). The 1.0mg dose was instead [REDACTED], as Jensen admitted. *Id.* (21:14-22:8).

In May 2009, Novo's head of GLP-1 development, [REDACTED], emailed Jensen with concerns from a Novo operations management committee ("DPComm") that [REDACTED] *Id.* (23:22-25:19); Ex2024. [REDACTED] sent long before Jensen's alleged conception, [REDACTED]. Ex1312 (26:8-14); Ex2024. Jensen cannot remember considering a 1.0mg dose before receiving that email. *Id.* (28:16-22).

² The earliest version of NCT773 is dated September 11, 2009. EX1014 at 11-13.

³ Petitioner assumes WO421's effective prior-art date is May 5, 2011.

Jensen again heard about the [REDACTED]

[REDACTED]. Ex1312 (44:9-46:18).

Days later, Jensen emailed Novo data modeler Daniël Jonker, describing

[REDACTED]:

Ex2026, 2 ([REDACTED]).

[REDACTED] Ex1312 (55:19-57:13).

[REDACTED] Ex2050,

¶¶ 21 - 22.

B. Antedating prior art requires direct and corroborating evidence of prior conception

An inventor can sometimes swear behind a reference by establishing prior conception and reduction-to-practice diligence. *See Apator Miitors ApS v. Kamstrup A/S*, 887 F.3d 1293, 1295 (Fed. Cir. 2018). Inventor testimony regarding conception must be corroborated by evidence “independent of information received from the inventor.” *Id.* (quoting *Hahn v. Wong*, 892 F.2d 1028, 1033 (Fed. Cir. 1989)). PO bears the burden of establishing an earlier effective filing date. *Apator*, 887 F.3d at 1297.

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Conception is “the formation, in the mind of the inventor of a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.” *REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016). Conception requires every claimed limitation, *id.*, but it does not include knowledge that the invention would work as intended, *Solvay S.A. v. Honeywell Int’l, Inc.*, 742 F.3d 998, 1000 (Fed. Cir. 2014) (*Solvay II*). Whether an invention will work as intended is instead relevant to reduction-to-practice. *Burroughs Wellcome Co. v. Barr Lab’ys*, 40 F.3d 1223, 1228 (Fed. Cir. 1994).

PO’s antedating arguments fail because: (1) Jensen’s declaration and deposition testimony do not show earlier conception, and (2) any earlier conception is not corroborated.

1. Jensen’s explanation does not show earlier conception

[REDACTED]

[REDACTED]. Instead, [REDACTED]. Ex1312 (21:14-22:8, 26:8-14); Ex2026, 2; Ex2024. Even if Jensen concluded that a 1.0mg dose would be appropriate, Ex2050, ¶6, that is not conception. Conception requires forming an idea, not recognizing another’s idea. *See Solvay S.A. v. Honeywell Int’l, Inc.*, 622 F.3d 1367, 1377-78 (Fed. Cir. 2010) (*Solvay I*) (conception requires an *original idea*). And Jensen’s conclusion that 1.0mg should be preceded by two lower doses to “[REDACTED]

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[REDACTED], Ex2050, ¶21, is not relevant because the disputed claims do not require dose escalation, any level of efficacy, or tolerability.

Jensen's "[REDACTED]" for the [REDACTED] [REDACTED] *id.* ¶22, is relevant to study design, not conception. The same goes for documents from a [REDACTED] meeting supposedly showing that Jensen's team [REDACTED]

[REDACTED]. *Id.* ¶¶23-26. Testing a dose "to confirm [it] would work for its intended use," *id.* ¶29, is not relevant to when or who conceived it. *See Solvay II*, 742 F.3d at 1000; *Medtronic, Inc. v. Teleflex Innovations S.A.R.L.*, 68 F.4th 1298, 1303 (Fed. Cir. 2023)).

2. There is no corroborating evidence of prior conception

Even assuming Jensen's declaration asserts earlier conception, it is not corroborated. PO's evidence shows only that [REDACTED] [REDACTED] not that she conceived the claimed invention before the effective date of the prior art. Moreover, even if PO's evidence were relevant to conception, it would not corroborate *Jensen's* prior conception because none of the evidence is specific to her versus other Novo employees.

Many of PO's documents cannot corroborate Jensen because they pre-date any supposed date of conception. *See* POR. 14-16 (citing Ex2070 (Phase I trial that

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began before Jensen joined Novo), Ex2022 (slides pre-dating Jensen’s purported conception), [REDACTED]
[REDACTED], Ex2050, ¶ 21)), Ex2027 (Jonker’s slides)).

Other evidence does not tie the idea of 1.0mg to Jensen. [REDACTED]
[REDACTED]
[REDACTED]
[REDACTED], Ex1312 (95:19-102:13))), [REDACTED] (summary of [REDACTED]
[REDACTED] with multiple participants), [REDACTED] (summary of [REDACTED] with no mention of Jensen). That consistent failure to connect Jensen to the 1.0mg dose is fatal to PO’s assertion of an earlier priority date because corroborating evidence must link the earlier conception to the inventor alleging conception. *Compare NFC Tech., LLC v. Matal*, 871 F.3d 1367, 1373-74 (Fed. Cir. 2017) (explaining that a “data sheet” sufficiently corroborated inventor testimony because, among other things, it included the inventor’s initials as its sole author) *with Weaver v. Houchin*, 467 F. App’x 878, 881 (Fed. Cir. 2012) (non-precedential) (documents listing additional authors failed to corroborate inventor testimony). PO’s additional evidence fails to corroborate Jensen because (1) none supports her explanation that [REDACTED] (even

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assuming that was “conception,” which it was not); and (2) all documents referring to a 1.0mg dose list multiple authors or meeting participants.

Dr. Flint’s declaration, Ex2051, likewise fails to corroborate Jensen’s alleged earlier conception for two reasons. First, it fails to assert any personal knowledge of the source of the 1.0mg dose—Flint merely attributes that dose to Jensen because [REDACTED].”

Ex2051, ¶5. And Flint admitted she was unaware [REDACTED]

[REDACTED] Ex1311 (50:3-52:13). Second, Flint’s litigation-driven testimony is not contemporaneous evidence of conception. *See Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1350-51 (Fed. Cir. 2001) (explaining post-invention testimony is “more suspect” than contemporaneous evidence because it is more likely to have a litigation-inspired motive). As for the evidence Flint cites, she admitted it does not demonstrate that the 1.0mg dose came from Jensen. Ex1311 (69:2-70:10, 77:3-78:1).

C. PO’s arguments about [REDACTED] inventorship are irrelevant

[REDACTED]
[REDACTED]
[REDACTED]
[REDACTED]. Nor can PO avoid the problem with its swear-behind evidence by arguing that inventorship is “of no moment here.” POR. 13 n.7. Jensen’s alleged

prior conception is an element of PO's defense. That is true regardless of what PO's evidence shows, [REDACTED]

[REDACTED]. Whether Jensen is a proper inventor is beside the point—PO's evidence fails to demonstrate *she* conceived of the claimed invention early enough to avoid the prior art.

III. WO421 ANTICIPATED CLAIMS 1-3

A. WO421 expressly teaches claim 1's dosing scheme

Claim 1 of the '462 patent is broad:

A method for treating [T2D], comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.

Ex1001 (35:42-44). PO disputes only whether WO421 teaches a 1.0mg dose supposedly because: (1) a POSA would understand WO421's 0.1-1.6mg range to include only doses subject to clinical testing; (2) a POSA would not envisage 1.0mg because the range included too many discrete doses; or (3) 1.0mg is critical despite the breadth of claim 1. Those arguments all fail.

1. 0.1-1.6mg includes 1.0mg

PO's argument that WO421's range excludes all doses except those in NCT657, POR. 20-22, ignores how POSAs would interpret a range in view of an ongoing trial. NCT657 was a dose-finding trial; POSAs understood it would result in a dose response curve for determining the effective doses. Ex1005 ¶¶ 95-97,

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282, 287-288. As the Board noted, Petitioner's expert Dr. Jusko testified that Phase 2 studies typically investigate a range of doses, including those predicted to be on the dose response curve plateau. Inst., 37 (citing Ex1005 ¶¶ 70-71). The choice not to include 1.0mg was not necessarily because it was outside the studied range—it meant only that the effectiveness of that dose could be estimated from the dose response curve, as Jensen herself admitted. Ex1312 (38:22-41:6). *See also* Ex1311 (27:21-28:13) ([REDACTED]). Ex1300, ¶¶ 263-268; Ex1301, ¶¶ 186-187.

Despite NCT657's dose-finding purpose, and Jensen's agreement with how POSAs use dose response curves, PO argues that POSAs would "interpret WO421 to disclose only the specific doses identified in NCT657." POR. 21. As support, PO raises Dr. Bantle's agreement that POSAs would look to NCT657 to understand the dose range in WO421, and his agreement that the 1.0mg dose was not in NCT657. POR. 21 (citing Ex2018 (78:9-19)). PO is wrong that those statements also mean that POSAs understood from NCT657 that 1.0mg was excluded from WO421's range. Ex1300, ¶¶ 192-196; Ex1301, ¶¶ 183-188. Bantle merely acknowledged that NCT657 itself did not identify 1.0mg within its range of tested doses. Neither Bantle nor Petitioner has asserted otherwise here.

PO's expert Dr. Rosenstock plays the same games when he asserts that Bantle "admits" a POSA "would have known that WO421 and NCT657 disclosed

‘the same dose range’ as one another.” Ex2010, ¶212 (quoting Ex2018 (71:5-13)). Bantle did *not* say that both references “disclosed” the same range, he said POSAs would “get the same dose range” from both references. Ex2018 (71:5-11). As he explained in his declaration, 1.0mg “falls within the range of doses” in NCT657. Ex1003, ¶326.

2. PO’s 1-in-320 theory ignores claim 1’s breadth and proves nothing even if accepted

a. Claim 1 covers 1/16 of the 0.1-1.6mg range regardless of how thin PO slices it

PO’s response dwells on its theory that claim 1 is limited to a single dose among WO421’s supposed “*at least 320*” distinct doses. POR. 22-29. That is wrong—POSAs would understand the 0.1-1.6mg range to include 16 discrete doses. Ex1300, ¶¶275, 287; Ex1301, ¶¶183-187. Regardless, PO’s argument fails because it ignores the proper scope of “1.0” to POSAs.

Neither party proposed construing “1.0mg.” Pet. 14; POR. 10; Inst. 23 (determining only preamble required construction). But PO’s argument that the claimed 1.0mg dose “encompasses only one of *at least 320 doses* in the [0.1-1.6mg] range,” POR. 28, requires an implicit construction making “1.0” much narrower than ordinary rounding principles would dictate. PO’s theory is that because some doses in the prior art supposedly differ by only .005mg, POR. 24-25,

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there are 320 distinct doses in the 0.1-1.6mg range, only one of which is the claimed 1.0mg dose.

PO's 1-in-320 theory requires the claimed 1.0mg dose to exclude the adjacent .995mg and 1.005mg doses in the supposed 320-dose range. That is nonsense. The "standard scientific convention" of rounding applies based on a number's mathematically significant figures. *Viskase Corp. v. Am. Nat'l Can Co.*, 261 F.3d 1316, 1320 (Fed. Cir. 2001); *see also AstraZeneca AB v. Mylan Pharms. Inc.*, 19 F.4th 1325, 1342 (Fed. Cir. 2021) (Taranto, J. dissenting) (explaining ordinary meaning of 0.001 is 0.0005-0.0014). To be sure, a patent can support a narrower scope, but the '462 patent includes no narrowing language, nor has PO argued for anything other than the ordinary meaning of "1.0." If anything, the '462 patent underscores normal rounding principles when it refers to consecutively higher doses as 1.0mg, 1.1mg, 1.2mg, etc. Ex1001 (3:43-45). Rosenstock also viewed the claimed dose to include only one single significant figure, but he admitted not taking that into account when discussing his 1-in-320 theory. Ex1313 (29:4-22; 235:8-18) (adding he formed no opinion about the breadth of "1.0mg").

Because the ordinary scope of 1.0 includes the range 0.95-1.04, the extent to which PO wants to slice the prior art range is irrelevant. Whether PO wants to include 16, 32, 320, or 3200 points, "1.0" covers 1/16 of them.

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b. WO421 anticipates Claim 1 even if WO421 describes 320 doses

PO's 1-in-320 theory does not overcome anticipation even if accepted. PO confuses a set of known discrete options, whether there be 16 or 320, with precedent involving a much larger class of potential options. POR. 22-23 (discussing *Mylan Pharms. v. Merck Sharp & Dohme Corp.*, 50 F.4th 147 (Fed. Cir. 2022)). In *Mylan v. Merck* the Federal Circuit affirmed the Board's finding of no anticipation by "a class of 957 predicted salts that may result from ... 33 disclosed compounds and eight preferred acids, some of which may not even form under experimental conditions," but the court placed no numerical limit on "limited class." 50 F.4th at 154. Here, there is no uncertainty about the existence of amounts between 0.1 and 1.6mg, and PO's purported 320 options are only a third of the nearly 960 potential but unpredictable salts in *Mylan v. Merck*. Whether there are 16 or 320 different doses, none would be difficult to envisage. Ex1300, ¶¶ 190-204; Ex1301, ¶¶ 188-208.

PO is also wrong that *Bristol-Myers Squibb Co. v. Ben Venue Lab's*, 246 F.3d 1368 (Fed. Cir. 2001), "reversed-in-part anticipation where the challenger did not establish that suitable premedicants consisted of only a few classes of compounds." (POR. 27) (internal quotes omitted). That decision *vacated* summary judgment because the record did not establish the size of a class of medications. 246 F.3d at 1380 (remanding for district court to consider how POSAs would have

viewed the prior art). And, as in *Mylan v. Merck*, the issue was not the size of an expressly disclosed range, it was how POSAs would understand the extent of only implicitly disclosed options. *Id.*

Finally, PO is wrong that Petitioner's experts "contradicted" the Board's statement at institution noting it was not clear why a POSA would look to the dosing of exenatide or lixisenatide versus semaglutide. POR. 23 (citing Inst. 32). PO cites statements about GLP-1 analogues generally, or that POSAs would consider other dosing regimens, but none of that contradicts the Board's skepticism that POSAs would look to exenatide or lixisenatide dosing over semaglutide. Inst. 32-33. That is healthy skepticism given how disproportionate the drug amounts in those dosing regimens are. The dosage strengths of exenatide are 5 or 10 µg and the dosage strengths of lixisenatide are 10, 15, or 20 µg. The largest of those doses, 20 µg, is much smaller than even the smallest dose in the prior art 0.1-1.6mg range. And PO ignores that only prior art exendin analogues (exenatide and lixisenatide) list doses in microgram amounts, while GLP-1 analogues (like semaglutide) are all dosed in milligrams. Ex1300, ¶¶ 182-190; Ex1301, ¶¶ 188-208.

3. 1.0mg is not critical to claim 1's broad treatment method

PO sidesteps WO421's straightforward teachings by arguing that 1.0mg was "critical." POR. 30-35. But there is nothing critical about 1.0mg in the context of claim 1, which requires only "treating" type 2 diabetes without "any particular

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level of efficacy.” Inst. 23 (adding that “treating” includes the “full spectrum” of treatments). Without any required treatment effect, or lack of side effects, there is no basis for PO’s criticality argument.

PO misreads *OSRAM Sylvania, Inc. v. American Induction Technologies, Inc.*, 701 F.3d 698, 705-06 (Fed. Cir. 2012), when it says a mere difference in operation is enough to show criticality. POR. 30-31 n.16. *OSRAM* said no such thing; it merely remanded for factual findings about *how* a POSA would view the difference between claimed and prior art ranges. 701 F.3d at 706. Furthermore, *OSRAM* involved more than a *difference* in operation—the prior art was “inefficient and impractical.” *Id.* And while *OSRAM* distinguished precedent where a claim limitation was not argued as critical or working differently, *OSRAM* did not say that merely working differently demonstrates criticality. *Id.* at 705-06 (distinguishing *ClearValue, Inc. v. Pearl River Polymers*, 668 F.3d 1340, 1344-45 (Fed. Cir. 2012)).

Atofina v. Great Lakes Chemical Corp., 441 F.3d 991 (Fed. Cir. 2006), is not to the contrary. The claimed range of 330-450°C there differed from the prior art 100-500°C range to the extent a reaction would not operate “as claimed” outside of the narrower temperature range. *See Ineos USA LLC v. Berry Plastics Corp.*, 783 F.3d 865, 869 (Fed. Cir. 2015) (discussing *Atofina*). Criticality demands more than *any* difference relative to the prior art, the question is whether

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the difference is “critical to the operability of the claimed invention.” *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020) (citing *Ineos*, 783 F.3d at 871). Neither the ’462 patent nor any other evidence suggests that 1.0mg is critical to treating T2D to any extent, which is all that claim 1 requires. Inst. 23.

PO’s expert applied the wrong criticality test. Relying on the specification, Rosenstock opined that *any* efficacy difference between two semaglutide doses proves criticality. Ex1313 (163:13-164:8) (“I already mentioned that the dosages from 0.1 to 1.6 are different. And my understanding is that meets the criticality.”), (173:22-174:17); Ex2010, ¶242 (“only ... doses of *0.8 mg or greater* showed improvements over once-daily liraglutide”); ¶245 (“only doses of 0.8 mg *and above*” reduced HbA1c to “level recommended by the American Association of Clinical Endocrinologists”); ¶246 (0.1, 0.2 and 0.4mg doses “did not result in statistically significant weight loss”). But the claims do not require efficacy better than liraglutide, satisfaction of a medical association’s glycemic target, or weight loss. Ex1300, ¶¶207-220; Ex1301, ¶¶210-226. Rosenstock further undermined PO’s criticality theory when he agreed that every semaglutide dose tested from 0.2 to 1.6mg statistically significantly reduced HbA1c compared to placebo. Ex1313 (153:8-18); Ex1001, Fig. 1 & 22:1-7. The claims require nothing more.

B. WO421 anticipates dependent claims 2 and 3

Claim 2 limits claim 1 to “parenteral” (non-oral) administration and claim 3 limits that non-oral administration to a subcutaneous solution injection. Both are taught by WO421. WO421 expressly refers to subcutaneous injection of semaglutide, and a POSA would understand such an injection to include a solution. Pet. 35-36. Furthermore, WO421 expressly discloses injectable formulations as “injectable solutions.” Ex1011, 40:23-26.

PO’s claim 2 argument about “improperly picking and choosing elements from disparate disclosures,” POR. 35, fails because WO421 expressly states that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg),” Ex1011, 44:13. If claim 1’s T2D treatment with a 1.0mg semaglutide dose is anticipated, claim 2’s parenteral administration is likewise anticipated because both teachings (dose and administration route) are taught by the same simple and clear disclosure. *See* Pet. 29-30, 35 (both citing Ex1011, 44:13). PO’s expert ignores the specific WO421 language cited by both of Petitioner’s experts. Ex1003, ¶271, Ex1005 ¶197.

PO’s argument regarding claim 3 fares no better. Claim 3 uses the term “the solution” with reference to claim 2, but neither claim 2 nor claim 1 refer to a solution. Ex1001 (35:42-48); Ex1003, ¶279 n.14. Despite that antecedent basis problem, claim 3 is clear because its subcutaneous injection is necessarily

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understood as a solution. Ex1003, ¶272; Ex1005, ¶200. That understanding is consistent with the '462 specification, which refers to “an injection solution” and a “dissolved” injected compound. Ex1001 (15:61-62, 9:5-6). PO nevertheless contends the injected semaglutide could be a suspension. POR. 36. If correct, that argument would raise an indefiniteness issue because whether the antecedent-basis-lacking phrase “the solution” is a separate limitation is unclear. As support for its suspension theory, PO cites Rosenstock’s reference to an article about injectable suspensions. Ex2010, ¶263 (citing Ex2004, 2). Far from casting doubt on Petitioner’s experts, that article reports that the “relatively few examples” of injectable suspensions required a large needle inappropriate for humans (the article discussed bovine injections), and it speculated about an alternative, “very difficult,” suspended-crystal approach. Ex2004, 2. That focus on cows, big needles, and suspended crystals underscores POSAs’ understanding that the injected doses taught by WO421 were solutions. Ex1300, ¶¶227-232; Ex1301, ¶¶235-241. Regardless, WO421 expressly refers to “injectable solutions,” Ex1011, 40:23-26, and thus anticipates even if PO’s suspension theory had any merit.

IV. Lovshin anticipates claims 1-3

PO’s arguments about Lovshin largely mimic its arguments about WO421 and are addressed above. POR. 37-40 (arguing that the 1.0mg dose was not in a

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trial or within Lovshin's 0.1-1.6mg range, which included 32 or 320 different doses; that 1.0mg was "critical"; and that Lovshin did not teach claims 2 and 3).

PO also argues that Lovshin supposedly did not teach T2D treatment. POR. 39-40. To the contrary, Lovshin taught that "[c]ontinuous subcutaneous administration of native GLP-1 to patients with type 2 diabetes ... lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss." Pet. 36-37 (quoting Ex1012, 1). The very title of Lovshin is "Incretin-based therapies for type 2 diabetes mellitus." Ex1012, 1. And by referring to NN9535 (semaglutide) as an incretin treatment being investigated at "0.1-1.6 mg once weekly," EX1012, 2 (Table 1), Lovshin taught T2D treatment with semaglutide. Pet. 37. PO may be arguing that Lovshin did not teach T2D treatment because it pointed to no T2D study (or perhaps no study with a 1.0mg semaglutide dose). POR. 39-40. Again, the lack of a studied dose does not undermine Lovshin's teachings. Moreover, Rosenstock acknowledged that POSAs "would have looked to publications regarding ongoing trials of [semaglutide], such as NCT657, to understand" Lovshin. Ex2010, ¶269. POSAs would have seen semaglutide used to treat T2D. Ex1013, 39-40; Ex1313 (196:8-19); Ex1300, ¶¶234-244; Ex1301, ¶¶244-253.

Bantle did not confirm Lovshin's supposed "proof failure." POR. 40. Bantle explained Lovshin's disclosure of T2D treatment with GLP-1 receptor agonists and

semaglutide as one such agonist. Ex1003, ¶¶99-102, 307 (referring to earlier discussion of Lovshin). Nor did Bantle “confirm” the absence of a semaglutide teaching when he said that Lovshin “further disclosed” information about exenatide, or that it “also disclosed” information about liraglutide. *Id.* ¶307.

V. Claims 1-10 would have been obvious under each of Grounds 3, 4, and 5

Treating T2D with a 1.0mg weekly dose of semaglutide would have been obvious under any of Petitioner’s Grounds 3, 4, or 5.⁴ Where the invention falls within a prior art range, the claims are prima facie obvious and the burden of production falls on PO to come forward with evidence of secondary considerations. Pet. 38-39 (citing *Galderma Lab’s v. Tolmar, Inc.*, 737 F.3d 731, 737-38 (Fed. Cir. 2012); *Genentech*, 946 F.3d at 1341). *Galderma* involved a claim to a composition for acne treatment with a composition including 0.3% of an active ingredient. 946 F.3d at 735. A prior teaching of a 0.01-1.0% range for the active ingredient was enough to shift the burden of production to the patentee to demonstrate secondary considerations. *Id.* at 738. PO does not respond to the presumption other than to argue that 1.0 is not within the range 0.1-1.6, echoing its anticipation argument, which is wrong for the reasons discussed above.

⁴ PO argues against motivation and reasonable expectation of success generally for all three grounds. POR. 41-69. Petitioner responds in kind and discusses PO’s arguments limited to specific grounds in section V.C.

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Beyond that prima facie obviousness conclusion applicable here, Petitioner further explained why POSAs would have been motivated to pursue a 1.0mg dose, and why they would have had a reasonable expectation of success. WO421, Lovshin, and published clinical trial protocols taught T2D treatment with once-weekly 0.1-1.6mg semaglutide doses. Pet. 39. Because clinical trials were underway, POSAs logically understood data must have supported the safety and efficacy of the tested range. Pet. 39-40. The remaining task was to evaluate doses within that range according to known techniques for finding optimal doses. Success would have been reasonably expected based on fundamental clinical design principles, including that the upper range of tested doses were likely to be efficacious and successful, Pet. 41 (citing Ex1005 ¶¶226-238), and experience with the related GLP-1 analogue liraglutide. Pet. 40. PO's counter-arguments demand too much proof while ignoring Petitioner's evidence.

A. PO's motivation arguments misunderstand Petitioner's grounds and the law

Contrary to PO's lead argument (POR. 41-42), Petitioner's obviousness grounds do not require modifying any reference. Selecting 1.0mg from WO421's 0.1-1.6mg range was routine optimization of a result-effective variable (Pet. 44), not a modification. The same is true for Lovshin. Pet. 50-51. And while NCT657 and NCT773 did not involve a 1.0mg dose, the purpose of those trials was to produce dose response curves based on a range of doses, from 0.1mg to 1.6mg

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(NCT657) or 1.2mg (NCT773). That range of doses encompassed 1.0mg. Pet. 54-57. As such, optimizing to 1.0mg is not a “modification” of those references either. But even if it were a modification of the tested doses, that would still be irrelevant. Nothing in Title 35 or precedent requires Petitioner to prove POSAs would have been motivated to alter a prior art embodiment. *Galderma*, 737 F.3d at 738.

PO argues that if POSAs were motivated to pursue any doses, it was only the tested doses, which PO again asserts were among 320 other doses in the prior art range. POR. 43-45. Put differently, PO effectively contends there were over three hundred *non-obvious* doses of semaglutide within the prior art 0.1-1.6mg range. That is absurd. There is no support for collapsing obviousness into anticipation. PO cannot avoid obviousness by slicing the prior art range into 320 distinct values because, even if there were 320, that number is not close to the magnitude that defeats normal optimization considerations.⁵ See *Genetics Inst., LLC v. Novartis Vaccines & Diagnostics*, 655 F.3d 1291, 1306 (Fed. Cir. 2011) (“very large” range of 68,000 prior art variants defeated obviousness argument).

Apparently recognizing the inconsistency between its 1-320 theory and Federal Circuit law on optimization, PO relies on two district court opinions that it

⁵ Also, for the reasons discussed above, if there were 320 distinct doses in the prior art range, 20 of them would have been within the scope of claim 1, which merely recites “1.0” and thus reads on any value that would round to 1.0.

misreads. POR. 46 (citing *Alcon Rsch., Ltd. v. Watson Labs.*, No. CV 15-1159, 2018 WL 1115090, at *22 (D. Del. Mar. 1, 2018) and *Alcon, Inc. v. Teva Pharms. USA*, 664 F. Supp. 2d 443, 461 (D. Del. 2009)). PO is wrong that *Alcon v. Watson* found a range of hundreds neither finite nor small. The issue there was the obviousness of selecting a “ternary system” from “hundreds of different” possible agents. 2018 WL 1115090, at *22. The court’s concern was not the hundreds of agents but the “*exponential number* of possibilities” for the claimed ternary system using those agents. *Id.* (emphasis added). And in *Alcon v. Teva*, the district court rejected the factual argument that there were only “five or six” candidates. 664 F. Supp. 2d at 461. It instead pointed to the “thousands of abstracts” and a witness’s search for options that “spanned years and a number of different conferences.” *Id.* The problem was that “the universe of ... compounds was not as succinctly identified” and included “myriad” options disclosed by the prior art. *Id.* There is no similarity between those cases and the obviousness of 1.0mg based on prior art teaching 0.1-1.6mg.

Optimization and criticality are also not the same. POR. 47. Even if 1.0mg were optimal for treating T2D, it is not critical because: (1) T2D can be treated with both lower and higher doses; and (2) claim 1 does not require any level of effectiveness. And while optimized variables may be critical to unexpected results,

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see In re Geisler, 116 F.3d 1465, 1470 (Fed. Cir. 1997), those were not proven here, as discussed below in section VI.C.

PO is further wrong that “to apply ‘routine optimization,’ the claimed value must be ‘optimum.’” POR. 49 (citing *SNF, S.A. v. Solenis Techs., L.P.*, IPR2020-01730, Paper 10, 15 (Apr. 22, 2021)). *SNF* does not state that proposition, which makes no sense in the first place. What matters is the *desire to optimize*. “The normal desire of artisans to improve upon what is already generally known can provide the motivation to optimize variables” *In re Ethicon, Inc.*, 844 F.3d 1344, 1351 (Fed. Cir. 2017). That motivation here was the desire to optimize semaglutide doses within the prior art range, which the clinical studies demonstrate. Ex1300, ¶¶259-276; Ex1301, ¶¶264-280. PO cannot avoid obviousness by suggesting that 1.0mg was not proven optimal, and thus inferior to another dose. *See In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (an obvious composition is not patentable simply because it is inferior to another composition). Nor is PO helped by arguing that Petitioner’s experts relied on hindsight to arrive at 1.0mg. POR. 49 (citing *SNF* at 15). Unlike the *SNF* experts, who did not explain their obviousness reasoning, *SNF* at 14, Petitioner’s experts explained their motivation reasoning in detail, and they did so for each obviousness ground. *See* Ex1003, ¶¶318-28, 355-66, 396-407 (Bantle’s motivation analysis of claim 1

under Grounds 3, 4, and 5); Ex1005, ¶¶224-29, 252-57, 280-84 (Jusko's motivation analysis of claim 1 under Grounds 3, 4, and 5).

Nor must Petitioner prove that POSAs would have been motivated to specifically select 1.0mg as the expected optimal dose—it is only necessary to show a motivation to optimize from among the prior art range of options. *See Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059-60 (Fed. Cir. 2019) (obviousness requires motivation to pursue the claimed invention “as one of several potential treatment options,” but not that the claimed invention would have been selected over those other options); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004) (prior art need only suggest obviousness of the combination, not that it is most desirable). Moreover, whether POSAs would have been motivated to pursue any particular dose should be measured against the scope of claim 1, which covers any degree of treatment. *See Janssen Pharms. v. Teva Pharms. USA*, 97 F.4th 915, 926 (Fed. Cir. 2024) (obviousness inquiry is driven by claim's objective reach) (citing *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 419 (2007)).

B. PO's reasonable-expectation-of-success arguments are unpersuasive

Beyond the motivation to optimize dosing, POSAs would have had a reasonable expectation of success in doing so. With prior art teaching T2D treatment with a range of semaglutide doses, and ongoing trials with different

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doses across that range, it can hardly be questioned that semaglutide dosing was a result effective variable, i.e., a variable that achieved a result. *In re Applied Materials, Inc.*, 692 F.3d 1289, 1295 (Fed. Cir. 2012). PO argues otherwise based on the lack of data, POR. 48, but that only meant POSAs would not have known *how* effective any dose was. Obviousness does not demand advanced knowledge of success, just a reasonable expectation of success. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1346 (Fed. Cir. 2021) (explaining data is not needed to reasonably expect success).

PO's constant drumbeat is that the obviousness grounds are supposedly based on the "mere existence" of trials, which cannot show a reasonable expectation of success absent data and often "fail." POR. 44-63 (referring to lack of clinical trial data or "mere" existence of trials no fewer than 25 times). But a reasonable expectation of success does not require confirmatory data. After all, such data would demonstrate anticipation. *Eli Lilly*, 8 F.4th at 1346. PO's evidence that "the vast majority of *all* Phase II trials fail" is a deeply flawed one-page article. POR. 51 (citing Ex2006); Ex1300, ¶¶ 100-105; Ex1301, ¶¶ 104-115. Regardless, before the priority date POSAs knew the Phase 2 semaglutide trial "demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide." Ex1282, 12; Ex1300, ¶¶ 106-112; Ex1301, ¶¶ 116-128. More

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importantly, PO cannot avoid obviousness by ignoring the very reasoning that formed the basis of Bantle's and Jusko's opinions.

The reasonable expectation of success in selecting 1.0mg from the prior art range came not just from the existence of trials, but from those trials' dosing schemes, which suggested a sweet spot of effective treatment without unwanted side effects between the narrow range of 0.8-1.6mg or 0.8-1.2mg. Ex1300 ¶¶295-311; Ex1301 ¶¶285-287, 297-298. This was on top of POSAs' extensive background knowledge of GLP-1 and its role in moderating human glucose levels, which had been known since the 1980s. Ex1003, ¶64; Ex1005, ¶76. Research into the use of GLP-1 and GLP-1 agonists to treat T2D ultimately led to the FDA's approval of exenatide in 2005 and liraglutide in 2010. Ex1005, ¶¶80, 87. POSAs would have known that liraglutide was the subject of numerous clinical studies and publications describing its effectiveness. Ex1003, ¶73. Liraglutide included amino acid residues that POSAs knew were essential for GLP-1 receptor binding. Ex1005, ¶84. They also knew about semaglutide's development, its structure, and that it included those amino acid residues. Ex1003, ¶¶78-79, 89-93. They also knew that liraglutide exhibited a classic, sigmoidal dose-response profile demonstrating increased efficacy with higher doses. Ex1005, ¶¶85-86, 238. POSAs were hardly relegated to reliance on the mere existence of trials.

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That additional evidence and knowledge in the art, which PO largely ignores, is significant. The Federal Circuit recently explained why. *See Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056 (Fed. Cir. 2024). The patent owner in *Salix* contested obviousness because the prior art lacked efficacy and safety data and was based, in part, on a clinical trial plan without the claimed dose. *Salix*, 98 F.4th at 1062. The court distinguished the case before it from a true mere-clinical-trial case where expectation of success might be in doubt because the disputed obviousness ground was based on more than a clinical trial plan—it was based on evidence showing that a different dose of the drug showed efficacy for a related use as well as other POSA knowledge.⁶ *Salix*, 98 F.4th at 1062-63. Even in the absence of trial data, that other evidence sufficed in *Salix* to show a reasonable expectation of success, which does not require certainty or absolute predictability. *Id.* at 1062. There is evidence beyond the clinical trials here too, including POSAs’ knowledge about the similarities between semaglutide and liraglutide, and the latter’s known efficacy to treat T2D at known doses, as discussed above.

⁶ The Federal Circuit’s hesitancy to conclude that a Phase II trial plan is enough to show a reasonable expectation of success, 98 F.4th at 1062, does not apply here for the separate reason that PO had announced the success of NCT657 before the critical date in a May 2009 SEC filing. Ex1282, 12 (semaglutide clinical efficacy and safety “was broadly in line with liraglutide”).

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While PO tries to drown out Petitioner's non-trial evidence with its "mere trials, no data" drumbeat, that other evidence was central to Petitioner's experts' reasoning. Rosenstock took up the same drumbeat when he faulted Jusko's position that POSAs would expect liraglutide and semaglutide to have a "similar dose response relationship," Ex1005, ¶238, just because they might not have the *same* dose response curve or different half-lives. Ex2010, ¶358; *see* Ex1301, ¶¶144-158, 302-303; Ex1300, ¶¶312-321. That is another "mere trials, no data" argument based on the lack of completed trials. The same is true for PO's arguments that the shape of semaglutide's dose response curve was "unknown," POR. 63-64. Again, PO is demanding too much. A successful trial and resulting dose response curve would have anticipated claim 1—Petitioner does not have to establish anticipation to demonstrate obviousness.

PO's argument that 72-82% of clinical trials fail flunks even minimal scrutiny. POR. 58-59. The three-paragraph article PO relies on identifies no trials, drugs, or definition of failure. To the extent "failure" reasons are suggested, the majority were "strategic," "not reported," or for "insufficient efficacy," e.g., "insufficient evidence of an efficacy advantage over a more advanced drug." Ex2006; Ex1313 (85:18-103:12). Where "failure" was reported, only 20% were related to pharmacokinetics, bioavailability, or safety. Ex2006. Similarly, PO's purported GLP-1 failures, POR. 61-62, were either not failures, not prior art, or

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both. Ex1300, ¶¶ 100-105, 123-127, 159-170; Ex1301, ¶¶ 104-115, 137-143, 159-179. The suspension of taspoglutide trials was attributed to the formulation, not the drug. Ex2061. Albiglutide was only withdrawn from the market in 2017 “due to limited prescribing” and “not due to any safety concerns.” Ex2063. *Before* the priority date, Rosenstock wrote that “[w]eekly albiglutide administration significantly improved glycemic control and elicited weight loss in type 2 diabetic patients, with a favorable safety and tolerability profile.” Ex2062, 1. PO cites nothing showing CJC-1134-PC was “never approved,” and cites only a 2023 print-out (Ex2064) showing Eli Lilly’s LY2428757 was never approved, while another Lilly drug listed in Lovshin (LY2189265) later became the blockbuster GLP-1 agonist Trulicity® (dulaglutide). Ex1012, 2; Ex2010 ¶¶ 199-200; Ex1313 (70:6-71:4; 72:5-75:6).

PO also contends POSAs would have “drawn *negative* inferences” and assumed “unfavorable” outcomes for the NCT657 and NCT773 trials based on a 2010 Novo annual report noting postponement of a semaglutide Phase 3 trial. POR. 67-69. PO leaves out that Novo was holding off on Phase 3 “pending a long-acting portfolio development *strategy decision*.” Ex2065, 26 (emphasis added). A Novo SEC filing *the next day* expressed Novo’s intent “to select among the two primary once-weekly GLP-1 candidates in the development portfolio, semaglutide and once-weekly liraglutide” in “mid-2012” to “allow for a more complete

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characterisation of once-weekly liraglutide.” Ex1131, 16. None of that suggests semaglutide trial results were unfavorable. Ex1300, ¶¶ 106-112; Ex1301, ¶¶ 72-75, 116-128. Importantly, a May 2009 Novo SEC filing reported the NCT657 trial outcome was *favorable*. Ex1282, 12 (semaglutide clinical efficacy and safety “was broadly in line with liraglutide”). It is disingenuous for PO to argue POSAs would have assumed NCT657 failed when PO publicly proclaimed the opposite.

PO also asserts Petitioner failed to show that experimentation was routine, and that testing every possible dose would have been burdensome given the number of doses in the 0.1-1.6mg range. POR. 51-52 (citing *Galderma S.A. v. Medy-Tox, Inc.*, PGR2019-00062, Pap.66, 30-32 (July 16, 2021)). Petitioner did not suggest testing *every* possible dose; it noted the prior art “had already winnowed down the doses to be tested to just a few.” Pet. 51-52. And as discussed *supra* at 8-9, generating a dose-response curve does not require testing every dose in a range. Further, as Petitioner’s experts explained, clinical trials, although expensive and time-consuming, would have been routine, and the prior art supplied ready-made semaglutide trial protocols. Ex1300, ¶ 285; Ex1301 ¶¶ 294-295; *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1367 (Fed. Cir. 2007) (“many techniques that require extensive time, money, and effort to carry out may nevertheless be arguably ‘routine’ to a POSA”).

C. PO's few arguments specific to particular obviousness grounds fail

1. Ground 3

PO's arguments about Ground 3 as applied to claims 1-3 cross reference its general arguments regarding obviousness, or its argument opposing anticipation of claim 2 and 3. POR 69-70. Petitioner has responded to those arguments above in sections V.A-B, III.B.

As for claims 4-10, PO asserts that Ground 3 included only conclusory assertions "with no explanation" of how or why POSAs would have "modified" WO421 or whether POSAs would reasonably expect success in doing so. POR. 70. But Petitioner's obviousness grounds do not contemplate any modifications to WO421. Claims 4-10 are directed to formulations, and WO421 expressly provides that its GLP-1 receptor agonists "may be prepared according to known formulation techniques," as Petitioner's formulation expert Dr. Dalby explained. Ex1007, ¶76 (citing Ex1011, 40:23-24). Petitioner explained each of claims 4-10 would have been obvious. *See* Pet. 48-50. The Petition cited to Dalby's declaration where he explained his reasoning, including his rationale for why there would have been a reasonable expectation of success. *Id.* PO cannot avoid obviousness by ignoring Petitioner's rationale and supporting expert testimony.

2. Ground 4

PO's arguments regarding Ground 4 have been addressed above, except for its argument that WO537's pharmacokinetic screening would not have been predictive of human outcomes because it focused on mice. POR. 71. PO's arguments are based on an article (Ex2005) written by an animal welfare advocate that does not address diabetic mouse models but criticizes the use of animal models generally. Ex1300, ¶¶ 91-99; Ex1301, ¶¶ 91-103. As Petitioner's experts explained, animal models, including diabetic mouse models, were well-established tools in the diabetes research field; PO's experts rely on them too. *Id.*; Ex1310 (43:22-45:5; 62:17-63:7). The Petition also explains that POSAs would have also looked to Lovshin, which provided information about human dosing. Pet. 50-51.

3. Ground 5

PO's arguments regarding Ground 5 fail for many of the reasons discussed above, and a few more. First, PO's attempt to avoid NCT773 based on Jensen's attempt to establish an earlier priority date, POR. 73-74, fail for the reasons discussed in section II.

Second, PO's argument that Ground 5 lacks the particularity required by 35 U.S.C. § 312(a)(3), POR. 74-75, is not an appropriate post-institution response. Section 312 is directed to the sufficiency of the petition, not the merits. Indeed, PO cites only institution denials in support of its § 312 argument. POR. 75 (citing *LG*

Elecs., Inc. v. Constellation Designs, LLC, IPR2022-01549, Paper 8, 8 n.1 (Apr. 20, 2023); *Adaptics Ltd. v. Perfect Co.*, IPR2018-01596, Paper 20 (Mar. 6, 2019) (informative)). If reaching Ground 5 is necessary, the Board should decide the merits of that ground, to which PO has responded, POR. 75-79

Third, PO repeats its general arguments about obviousness, POR. 76, 79, that Petitioner responds to above in sections V.A-B.

Finally, PO's arguments about Japanese test subjects fail. Claim 1 is agnostic to nationality or race, and even if PO is correct that a POSA would only consider the reduction in the maximum dose to 1.2mg relevant to the Japanese population, PO cannot defeat obviousness by implicitly arguing that Petitioner's obviousness theory is limited to that population. *See Bayer Healthcare Pharms. v. Watson Pharms*, 713 F.3d 1369, 1376 (Fed. Cir. 2013) (rejecting argument about prior art being directed to specific patient populations where claims did not distinguish between populations). Ex1300, ¶¶ 365-366; Ex1301, ¶¶ 354-355.

VI. PO'S SECONDARY-CONSIDERATIONS ARGUMENTS CANNOT SAVE CLAIMS 1-10

PO bears the burden of production with respect to evidence of secondary considerations of nonobviousness. *ZUP, LLC v. Nash Mfg.*, 896 F.3d 1365, 1373 (Fed. Cir. 2018). PO's various secondary-considerations arguments fail at least because they are inconsistent with law and overstate the facts. Moreover, secondary considerations evidence, even if proven, does not always overcome a

strong prima facie obviousness case. *Perfect Web Techs., Inc. v. InfoUSA*, 587 F.3d 1324, 1333 (Fed. Cir. 2009). Here, where the claim is broad and the only missing limitation—assuming the prior art does not anticipate—is a dose falling squarely within a prior art range, the prima facie obviousness case is strong. PO’s secondary considerations arguments fail to demonstrate non-obviousness.

A. Nexus

“[E]vidence of secondary considerations must have a nexus to the claims, *i.e.*, there must be a legally and factually sufficient connection between the evidence and the patented invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019) (cleaned up). While there is a rebuttable presumption of nexus when the objective evidence is tied to a specific product that embodies and is coextensive with the claimed invention, *id.*, when that evidence results from something other than what is both claimed and *novel*, “there is no nexus to the merits of the claimed invention,” *Merck & Cie v. Gnosis S.P.A.*, 808 F.3d 829, 837 (Fed. Cir. 2015).

Nexus cannot be presumed here, at least because PO repeatedly describes unclaimed features of 1.0mg Ozempic® as critical. A “patent claim is not coextensive with a product that includes a ‘critical’ unclaimed feature that is claimed by a different patent and that materially impacts the product’s functionality.” *Fox Factory*, 944 F.3d at 1375. PO repeatedly describes weight loss

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as a critical feature of 1.0mg Ozempic®. Ex2054, ¶¶47, 61-62, 68, 82; Ex2055, ¶31. But weight loss is not an element of the '462 claims. *E.g.*, Ex1313 (18:3-19:12); Ex1310 (57:22-58:6). PO has a different patent—U.S. Patent No. 9,764,003—that claims “a method for reducing body weight” by “administering semaglutide once weekly in an amount of at least 0.7 mg and up to 1.6 mg to a subject in need thereof.” Ex2002 (35:30-35). PO never addresses the '003 patent, and its secondary considerations experts were unaware of it. Ex1140 (15:7-13; 78:6-17); Ex1310 (57:22-58:13); Ex1314 (12:11-18). PO also relies on secondary considerations concerning “cardiovascular outcomes” and “kidney-protective effects.” Ex2055, ¶33; EX2011, ¶44. But those effects are the subject of a patent application claiming use of once-weekly semaglutide doses “of 0.05-2.0 mg” for “reducing the risk of a major adverse cardiovascular event” “wherein the subject has type 2 diabetes and cardiovascular disease.” Ex1296, 1, 11, 21-24 ('032 Appl. Claims and Response; Hvelplund Declaration); Ex1304, ¶¶127-130. Dependent claims in the '032 application also tie the subject’s “cardiovascular disease” to “chronic renal impairment.” *Id.* (Claim 17). Ex1296, 1, 12-13, 24-25; Ex1306 ¶¶115-118.

“Where a product embodies claims from two patents, a presumption of nexus can be appropriate only if the claims of both patents generally cover the same invention.” *Fox Factory*, 944 F.3d at 1375-77 (no co-extensivity where

“unclaimed features ... go to the heart of another one of [PO’s] patents”). The ’462 patent (method for treating T2D), ’003 patent (method for reducing body weight), and ’032 application (method of reducing risk of major adverse cardiovascular event) do not all generally cover the same invention, so no nexus presumption applies.

Alternatively, PO argues that evidence related to each alleged secondary consideration is “the direct result of the unique characteristics of the claimed invention.” POR. 80 (cleaned up). As explained below, that is wrong.

B. Commercial success

PO trumpets the “immense” commercial success of Ozempic® since its 2018 launch, [REDACTED]. POR. 81. And while it admits that success flowed “in substantial part” from its advertising campaign, PO argues that its advertising was merely highlighting benefits realized by its ’462 patent. POR. 82. To be sure, “Ozempic®” has significant sales. The question is whether those sales support an economic inference of non-obviousness. They do not. Ex1308 ¶¶ 13-16, 70, 89-91.

“If commercial success is due to an element in the prior art, no nexus exists.” *Merck & CIE*, 808 F.3d at 838 (citation omitted). Using once-weekly subcutaneous semaglutide injections to treat T2D is indisputably in the prior art. E.g., Ex1011; Ex1012; Ex1013; Ex1300 ¶¶ 68-70, 74-77. And PO’s prior art U.S.

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Patent Nos. 8,129,343 and 8,536,122 claim the semaglutide molecule and its use to treat T2D. Ex1068 (claims 1-6); Ex1067 (claims 1-2, 4-11, 15) Ex1302, ¶¶ 275-276. The only '462 claim element PO contends is *not* prior art is the 1.0mg dose. But semaglutide's once-weekly dosing and T2D efficacy, touted by PO as commercial success drivers, are due to its molecular structure, not the 1.0mg dose. Ex1302 ¶¶ 227, 289. Literature relied on by PO's experts confirms this. Ex2082, 8; Ex2083, 2; Ex1140 (53:1-55:19; 62:2-20; 73:4-10). So does the fact that semaglutide is approved to treat T2D at doses other than 1.0mg, namely, 0.5 and 2.0mg. Ex2076, 3-4; Ex1140 (31:9-32:12, 34:2-5; 35:17-36:1) (explaining "Ozempic has multiple approved dosages, which allows me to tailor treatment to patients as their needs change over time"); Ex1302, ¶¶ 220-222; Ex1308, ¶¶ 36-44.

PO similarly has no legal basis for assigning Ozempic®'s commercial success specifically to the 1.0mg dose. Dr. Vellturo relied on PO's expert Dr. Goland to show nexus. Ex2300, ¶¶ 7, 11, 82-83; Ex1314 (10:19-12:18). But Goland did not review *any* prior art to the '462 patent and did not know there were "earlier patents for semaglutide ... prior to [the '462] patent." Ex1140 (26:10-19; 11:3-6; 15:7-13; 18:1-19:18). Goland was thus in no position to opine on nexus, undermining both her testimony and Vellturo's. *See UCB, Inc. v. Actavis Laby's UT*, 65 F.4th 679, 696 (Fed. Cir. 2023) (faulting expert for "not analyz[ing]

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whether UCB's multiple patents were responsible for commercial success"); Ex1308, ¶¶29-35.

PO also alleges Ozempic[®] is commercially successful because its tolerability and convenience promotes patient compliance. POR. 82; Ex2300, ¶¶30-32, 82, 96, 103, 105. But as Goland conceded, Ozempic[®]'s tolerability is due to an unclaimed titration regimen. Ex1140 (36:15-37:17); Ex1302, ¶219. And as discussed above, Ozempic[®]'s once-weekly dosing is both in the prior art and attributable to the active ingredient, not a 1.0mg dose. Ex1308, ¶¶36-44; Ex1302, ¶289; Ex1140 (73:4-10). PO also fails to account for Ozempic[®] demand based on weight loss (including when used off-label) that is claimed in the '003 patent, not the '462. Ex1308, ¶¶45-46, 49-58; Ex1140 (89:19-90:8).

PO also tries to rebut any argument that Ozempic[®]'s success was due to exclusivity created by other patents. POR. 82-83. That is wrong. Blocking patents can "diminish[] possible rewards from a non-owner's or non-licensee's investment activity aimed at an invention whose commercial exploitation would be infringing," leading to a "decrease in incentives [that] can discount the significance of evidence of commercial success and long-felt need." *Janssen*, 97 F.4th at 935-36 (cleaned up); *Acorda Therapeutics v. Roxane Lab'ys*, 903 F.3d 1310, 1337 (Fed. Cir. 2018) (collecting cases). Here, at least PO's '343 and '122 patents

claiming the semaglutide molecule and its use to treat T2D are quintessential blocking patents. Ex1308, ¶¶ 71-85; Ex1302, ¶¶ 275-276.

PO is wrong to limit the effect of blocking patents to their issue date. POR 83. The public was aware as early as September 2006 that PO was seeking U.S. patent protection for the semaglutide inventions that would later issue as the '343 and '122 patents. Ex1308, ¶¶ 76-79. That impending exclusivity would have disincentivized development of the claimed subject matter years before the priority date. Ex1308, ¶¶ 82-84. Another PO patent, U.S. Patent No. 8,114,833, covering certain formulations of GLP-1 compounds (including semaglutide), published even earlier. Ex1308, ¶¶ 80-84; Ex1302, ¶ 277; Ex1209, 1. These multiple blocking patents render PO's commercial success arguments weak at best.

C. Unexpected results

PO argues "superior" results of its claimed method, including for glucose control and weight loss, amounted to unexpected results that a POSA would have thought possible only through bariatric surgery. POR. 84.

PO's experts failed to measure unexpected results against *the closest prior art*, which is the "starting reference point for evaluating unexpectedness." *Janssen*, 97 F.4th at 933. The closest prior art here is the 0.8mg semaglutide dose identified in NCT657 (Ex1013) or the 1.8mg dose of the structurally-similar GLP-1 agonist liraglutide. Ex1302, ¶¶ 205-208; Ex1002, 344-45. PO's experts instead compared

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Ozempic® 1.0mg to insulin glargine, sulphonylureas, meglitinides, metformin, dulaglutide, exenatide ER, and the lower 1.2mg liraglutide dose. POR. 84; Ex2054, ¶¶61-74; Ex1140 (22:7-23:15; 25:1-26:8; 50:6-51:1; 65:20-66:16; 71:19-72:1); Ex1310 (15:9-16:8); Ex1258 (12:5-17).

When assessing unexpected results, a “difference of degree is not as persuasive as a difference in kind—i.e., if the range produces ‘a new property dissimilar to the known property,’ rather than producing a predictable result but to an unexpected extent.” *UCB*, 65 F.4th at 693. None of PO’s experts understood or considered this legal principle. *See* Legal Standards sections in Ex2011 (¶¶21-26) & Ex1310 (15:4-8); Ex2054 (¶¶19-26) & Ex1140 (12:19-13:1); Ex2055 (¶¶13-20) & Ex1258 (10:6-20); *see also* Ex1140 (51:10-20 (agreeing HbA1c and weight reduction differences between semaglutide 1.0 mg and liraglutide 1.2mg are ones of degree)); Ex1258 (74:16-75:1 (compared to “other therapies” semaglutide showed a greater cardiovascular “degree of benefit”)). Petitioner’s experts did the proper analysis and explained the allegedly unexpected differences were ones of degree related to *known* GLP-1 agonist properties (i.e., class effects), not ones of kind. Ex1302, ¶¶252-257; Ex1304, ¶¶135-140, 150-159; Ex1306, ¶¶139-144.

PO also asserts unexpected kidney and heart results that allegedly flowed from “superior efficacy” of the 1.0mg dose or were “more robust” or showed “more benefit” than other semaglutide or liraglutide doses. POR. 84-86. First,

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when assessing unexpected results, “evidence of superior efficacy does not undercut a reasonable expectation of success.” *UCB*, 65 F.4th at 693 (citing *Hoffman-La Roche Inc. v. Apotex Inc.*, 748 F.3d 1326, 1331, 1333-34 (Fed. Cir. 2014)). Second, PO refers repeatedly to percentage differences in known properties between agents with no evidence that the differences are ones of kind, not degree. POR. 85 & Ex2015, 8, Ex1310 (51:11-52:20). Third, some studies PO relies on to show kidney benefits *excluded* T2D patients and did not use a 1.0mg semaglutide dose, but nonetheless confirmed *multiple* doses exhibit kidney benefits (some being *better* than 1.0mg). Ex2013, 2-3; Ex1310 (58:14-60:15); Ex1306, ¶¶ 106-107, 111, 158-159. And PO’s kidney expert’s declaration was riddled with flaws. Ex1306, ¶¶ 23-25, 29, 135-138, 151; Ex1310 (11:9-17:14).

The cardiovascular benefits associated with Ozempic® were also not unexpected. Ex1304, ¶¶ 118-145. They were in the prior art with extensive preclinical models and human clinical data spanning more than a decade. Ex1304, ¶¶ 74-98; Ex1066, Ex1148, Ex1229-1244, Ex1251-1252, Ex1278. Those benefits were entirely expected, particularly when measured against the closest prior art (an exercise Dr. Blaha did not undertake).⁷ Ex1304, ¶¶ 119-122. And while heterogeneity exists in GLP-1 agonist clinical endpoints, liraglutide, dulaglutide,

⁷ Dr. Blaha did not know semaglutide was in the prior art. Ex1258 (12:18-13:19; 15:1-17).

and the 0.5mg semaglutide dose all demonstrate the same types of cardiovascular benefits. Ex1304, ¶¶ 99-102, 135-140. Moreover, that these same types of results are seen across the approved maintenance doses for Ozempic[®] demonstrates the drug, not the dose, is the reason for cardiovascular benefits. Ex1304, ¶¶ 135-140, ¶¶ 150-159; Ex2102, 44-53.

D. Long-felt need

PO argues Ozempic[®] satisfied a long-felt need for a “safe, effective, and tolerable once-weekly T2D treatment” with significant weight loss. POR. 87-88. But Ozempic[®] was not the first safe, effective, and tolerable once-weekly GLP-1 agonist; the claims require no particular efficacy level; and Ozempic[®]’s tolerability results from an unclaimed titration regimen. Ex1302, ¶¶ 219, 285-286; Ex1310 (70:12-17); *see supra* 38. While patients may prefer once-weekly dosing, once-weekly semaglutide dosing appears throughout the prior art and is attributable to the molecule, not a 1.0mg dose. *Supra* 36-37. PO’s argument about weight gain from other therapies are based on medications *other than* GLP-1 agonists, which as a class were known to *reduce* weight. Ex1302, ¶¶ 135-140; Ex1140 (72:7-18). And for the same reasons PO’s blocking patents on using semaglutide to treat T2D undercut commercial success, they undercut long-felt need, too. *Supra* section VI.B; *Janssen*, 97 F.4th at 935-36.

E. Industry praise and skepticism

Novo contends Ozempic® has received “industry praise” in medical journals, citing exhibits 2082-2085. Each describes trials sponsored and paid for by PO and include PO’s employees as authors, undermining any inference of *industry* praise. Ex2082 at 1, 9; Ex2083 at 1; Ex2084 at 1; Ex2085 at 1, 8; *Bayer*, 713 F.3d at 1377 (rejecting patentee’s “self-referential” “published efficacy studies” as evidence of praise). PO’s other industry praise evidence boils down to *New Yorker* and *New York Times* articles. Ex2080, Ex2081. As a cursory review shows, those articles are primarily about obesity, weight loss, and potential uses of GLP-1 agonists *other than* treating T2D, and say nothing about a 1.0mg dose of semaglutide. Ex1302, ¶¶ 291-306. PO’s reliance on medical guidelines suggesting use of semaglutide related to cardiovascular risks also fails to establish praise. The guidelines recommend using *any* GLP-1 agonist with proven cardiovascular benefit, including liraglutide, dulaglutide, and semaglutide, or an SGLT-1 inhibitor. They never make a specific recommendation to use semaglutide, much less the 1.0mg dose. Ex1304, ¶¶ 150-159.

PO’s “industry skepticism” is just Goland’s choice to delay prescribing Ozempic® for a few months “until post-marketing reports and data were available.” POR. 90 (citing Ex2054, ¶¶ 88-92). That is not “industry skepticism,” especially

after Goland conceded her colleagues didn't share her skepticism and began using Ozempic® immediately upon approval. Ex1140 (98:19-100:6).

VII. CONCLUSION

For the reasons in the Petition and here, the Board should find the challenged claims unpatentable.

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Dated: May 22, 2024

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CERTIFICATE OF WORD COUNT UNDER 37 C.F.R. § 42.24(d)

Under 37 C.F.R. § 42.24(d), the undersigned certifies that the word count for this Reply totals 9,582 words, excluding the parts exempted by 37 C.F.R. § 42.24(c) and thus complies with that rule as modified by the Board's January 9, 2024 Order (Paper 27). The word count was made using the built-in word count function in the Microsoft Word software used to prepare this document.

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that I caused to be served a true and correct copy of the foregoing: PETITIONER'S REPLY and accompanying Exhibits by email to the electronic service addresses for Patent Owner and Petitioner in IPR2024-00009:

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