

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC., DR REDDY'S LABORATORIES,
INC., DR. REDDY'S LABORATORIES, LTD., SUN PHARMACEUTICAL
INDUSTRIES LTD., AND SUN PHARMACEUTICAL INDUSTRIES, INC.,
Petitioners,

v.

NOVO NORDISK A/S,
Patent Owner

Case IPR2023-00724
Patent 10,335,462

PATENT OWNER'S SUR-REPLY

LIST OF EXHIBITS

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EX2004	Miller, M., et al., “Low Viscosity Highly Concentrated Injectable Nonaqueous Suspensions of Lysozyme Microparticles,” <i>Langmuir</i> , Author Manuscript (2011), PMC 2011 (Feb 17)
EX2005	Knight, A., “Systematic Reviews of Animal Experiments Demonstrate Poor Contributions Toward Human Healthcare,” <i>Reviews on Recent Clinical Trials</i> , Vol.3, Issue 2, 89-96 (2008)
EX2006	Arrowsmith, J., “Phase II failures: 2008–2010,” <i>Nature Reviews, Drug Discovery</i> , Vol. 10 (May 2011)
EX2007	Excerpt of Novo Nordisk’s Initial Responses to Defendants’ Initial Invalidity Contentions Regarding U.S. Patent Nos. 8,129,343; 8,536,122; 8,114,833; 8,920,383; 9,775,953; 9,457,154; and 10,335,462, <i>In re: Ozempic (Semaglutide) Patent Litigation</i> , No. 1:22-cv-01040-CFC, (D. Del. Dec. 21, 2022)
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EX2012	Rossing, P., et al., “The rationale, design and baseline data of FLOW, a kidney outcomes trial with once-weekly semaglutide in people with type 2 diabetes and chronic kidney disease,” <i>Nephrol Dial Transplant</i> , Vol.38, 2041-2051 (2023)
EX2013	Heerspink, H., et al., “Effects of Semaglutide on Albuminuria and Kidney Function in People with Overweight or Obesity With or Without Type 2 Diabetes: Exploratory Analysis from the STEP 1, 2 and 3 Trials,” <i>Diabetes Care</i> , Vol.46, Issue 4, 801-810 (2023)
EX2014	Weeda, E., et al., “Medication adherence to injectable glucagon-like peptide-1 (GLP-1) receptor agonists dosed once weekly vs once daily in patients with type 2 diabetes: A meta-analysis,” <i>Int J Clin Pract.</i> , Vol.75 (2021)

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EX2015	Shaman, A., et al., “Effect of the Glucagon-Like Peptide-1 Receptor Agonists Semaglutide and Liraglutide on Kidney Outcomes in Patients With Type 2 Diabetes: Pooled Analysis of SUSTAIN 6 and LEADER,” <i>Circulation</i> , Vol.145, 575-585 (2022)
EX2016	Mehdi, S., et al., “Glucagon-like peptide-1: a multi-faceted anti-inflammatory agent,” <i>Frontiers in Immunology</i> , Vol. 14 (2023)
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EX2062	Rosenstock, J., et al., “Potential of Albiglutide, a Long-Acting GLP-1 Receptor Agonist, in Type 2 Diabetes,” <i>Diabetes Care</i> , Vol.32, Issue 10, 1880-1886 (October 2009)
EX2063	OPTUMRx, “Tanzeum® (albiglutide) – Drug Discontinuation,” available at https://professionals.optumrx.com/content/dam/optum3/professional-optumrx/news/rxnews/drug-recalls-shortages/drugwithdrawal_tanzeum_2017-0801.pdf (2017)
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EX2075	Madsbad, S. et al., "Improved Glycemic Control With No Weight Increase in Patients With Type 2 Diabetes After Once-Daily Treatment With the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)," <i>Diabetes Care</i> , Vol.27, Issue 6, 1335-1342 (June 2004)
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EX2078	Blüher, M. et al., "Dose-response effects on HbA1c and bodyweight reduction of survodutide, a dual glucagon/GLP-1 receptor agonist, compared with placebo and open-label semaglutide in people with type 2 diabetes: a randomized clinical trial," <i>Diabetologia</i> (2023), available at https://link.springer.com/content/pdf/10.1007/s00125-023-06053-9.pdf
EX2079	United States Patent and Trademark Office, Consolidated Trial Practice Guide, Appendix B Default Protective Order (November 2019)
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EX2081	Dani Blum, "What's Next for Ozempic," <i>New York Times</i> , December 20, 2023
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EX2083	V. Aroda <i>et al.</i> , "Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naïve patients with type 2 diabetes (SUSTAIN 4): a

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EX2084	R. Pratley <i>et al.</i> , “Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomized, open-label, phase 3b trial,” <i>Lancet Diabetes Endocrinol</i> 6:275-86 (2018)
EX2085	A. Ahmann <i>et al.</i> , “Efficacy and Safety of Once-Weekly Semaglutide Versus Exenatide ER in Subjects with Type 2 Diabetes (SUSTAIN 3): A 56-Week, Open-Label, Randomized Clinical Trial,” <i>Diabetes Care</i> 2018;41:258-266
EX2086	Abdul-Ghani, M., <i>et al.</i> , Cardiovascular Disease and Type 2 Diabetes: Has the Dawn of a New Era Arrived?, <i>Diabetes Care</i> , 40:813-820 (2017).
EX2087	ADA Standards of Medical Care., Cardiovascular Disease and Risk Management: Standards of Medical Care in Diabetes, <i>Diabetes Care</i> 45(Suppl. 1):S144–S175 (2022)
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EX2090	Cosentino, F. <i>et al.</i> , ESC Guidelines on diabetes, pre-diabetes, and cardiovascular diseases developed in collaboration with the EASD, <i>Eur. Heart J.</i> , 41:255-323 (2019)
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EX2093	Davies, M.J., <i>et al.</i> , Cardiovascular outcomes trials: a paradigm shift in the current management of type 2 diabetes, <i>Cardiovasc. Diabetol.</i> , 21:144 (2022)
EX2094	Eckel, R.H. and Blaha, M.J., Cardiometabolic Medicine: A Call for a New Subspecialty Training Track in Internal Medicine, <i>Am. J. Med.</i> , 132(7):788-790 (2019).
EX2095	Evans, L.M., <i>et al.</i> , A population-adjusted indirect comparison of cardiovascular benefits of once-weekly subcutaneous semaglutide and

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EX2098	Jha, K.K., <i>et al.</i> , Transitioning to GLP-1 RAs and SGLT2 Inhibitors as the First Choice for Managing Cardiometabolic Risk in Type 2 Diabetes, <i>Curr. Atheroscler. Rep.</i> , 24:925-937 (2022)
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EX2100	Leiter, L.A., <i>et al.</i> , Cardiovascular risk reduction with once weekly semaglutide in subjects with type 2 diabetes: a post hoc analysis of gender, age, and baseline CV risk profile in the SUSTAIN 6 trial, <i>Cardiovasc. Diabetol.</i> , 18:73 (2019)
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EX2104	Maskery, M.P., <i>et al.</i> , Glucagon-like peptide-1 receptor agonists as neuroprotective agents for ischemic stroke: a systematic scoping review, <i>J. Cereb. Blood Flow Metab.</i> , 41:14-30 (2020)
EX2105	Nauck, M.A., <i>et al.</i> , Cardiovascular Actions and Clinical Outcomes With Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors, <i>Circulation</i> , 136: 849-870 (2017)
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EX2111	Verma, S., <i>et al.</i> , Effects of glucagon-like peptide-1 receptor agonists liraglutide and semaglutide on cardiovascular and renal outcomes across body mass index categories in type 2 diabetes: Results of the LEADER and SUSTAIN 6 trials, <i>Diabetes Obes. Metab.</i> , 22:2487-2492 (2020)
EX2112	Terry, T., <i>et al.</i> , Does aggressive glycemic control benefit macrovascular and microvascular disease in type 2 diabetes? Insights from ACCORD, ADVANCE, and VADT, <i>Curr. Cardiol. Rep.</i> , 14(1):79-88 (2012).
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EX2352	Mayo Clinic, “Diabetes – Symptoms & causes,” https://www.mayoclinic.org/diseases-conditions/diabetes/symptoms-causes/syc-20371444 , last updated Sept. 15, 2023.
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EX2354	Centers for Disease Control and Prevention, “Gestational Diabetes,” https://www.cdc.gov/diabetes/basics/gestational.html , last reviewed Dec. 30, 2022.
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EX2357	National Institute of Diabetes and Digestive Kidney Diseases, “Type 2 Diabetes,” https://www.niddk.nih.gov/health-information/diabetes/overview/what-is-diabetes/type-2-diabetes , last reviewed May 2017.
EX2358	Mayo Clinic, “Type 2 diabetes – Diagnosis & Treatment,” https://www.mayoclinic.org/diseases-conditions/type-2-diabetes/diagnosis-treatment/drc-20351199 , last updated March 14, 2023.
EX2359	Moses, R.G., Combination Therapy for Patients with Type 2 Diabetes: Repaglinide in Combination with Metformin, Overview of Oral Antidiabetic Medications, https://www.medscape.com/viewarticle/722513_3
EX2360	Quianzon, C. C.L. and Cheick, I.E., History of current non-insulin medications for diabetes mellitus, <i>J. Community Hosp. Intern. Med. Perspect.</i> 2012 Oct. 15; 2(3). Doi: 10.3402/jchimp.v2i3.19081.
EX2361	National Institute of Diabetes and Digestive and Kidney Diseases, “Low Blood Glucose (Hypoglycemia),” https://www.niddk.nih.gov/health-information/diabetes/overview/preventing-problems/low-blood-glucose-hypoglycemia , last reviewed July 2021.
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EX2367	Sirtori, C.R. and Pasik, C., Re-evaluation of a biguanide, metformin: mechanism of action and tolerability, <i>Pharmacol. Res.</i> 1994 Oct-Nov; 30(3):187-228.
EX2368	Tomkin, G.H., Treatment of type 2 diabetes, lifestyle, GLP1 agonists and DPP4 inhibitors, <i>World J. Diabetes</i> , 2014 Oct. 15; 5(5):636-650.
EX2369	U.S. Food & Drug Administration, Drugs@FDA, Glucophage®
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EX2371	U.S. Food & Drug Administration, Drugs@FDA, Prandin®
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On Reply (“Rep.”¹), Petitioner still fails to carry its burden. The Grounds fail for the POR’s reasons and those below responding to Petitioner’s Reply.

I. Grounds 1 and 3: WO421 Is Not Prior Art to Claims 1-3

Petitioner doesn’t dispute that, *before* WO421, Jensen had the claimed invention in mind [REDACTED]. Petitioner only disputes Jensen’s *conception*, arguing (1) others mused aloud about “1.0 mg” (without any definite or permanent idea of the complete and operative invention) and (2) Petitioner would require more than the already-voluminous corroborating evidence. Both arguments fail.

A. Jensen’s Conception

Undisputedly, by March 17 and no later than May 28, 2010, Jensen formed “a *definite and permanent idea* of the *complete and operative invention*” of claims 1-3. *E.g.*, *REG Synthetic Fuels, LLC v. Neste Oil Oyj*, 841 F.3d 954, 962 (Fed. Cir. 2016) (emphases modified). Petitioner’s Reply ignores ’462’s “treating” requires expectations of both *efficacy* and *tolerability*. EX2556, 88:8-18 (requires acceptable safety/tolerability/efficacy); EX2553, 14:7-15:4 (“if the patient won’t

¹ Unless stated, statutory and regulatory citations are to 35 U.S.C. or 37 C.F.R., as context indicates, internal citations omitted, abbreviations are as the POR defined, and emphases/annotations are added.

accept treatment, then it’s not a treatment”), 41:3-15 (“statistically insignificant [HbA1c] decrease” “[p]robably not” claimed “treating”); EX2010, ¶¶240-258; Pet.14-15 (“to *alleviate or reduce* [T2D] symptoms and complications...”); Inst.23; POR.10-11; *see* EX2019, 128:6-16 (“goal is to have as much efficacy without toxicity”).² And Jensen finally reached conception by [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]. EX2050, ¶¶21-26; EX1312, 71:6-8.

This testimony is amply corroborated (§I.B)—including by, *inter alia*, contemporaneous “evidence...specific to her” (*cf.* Rep.5) documenting *Jensen’s* [REDACTED]

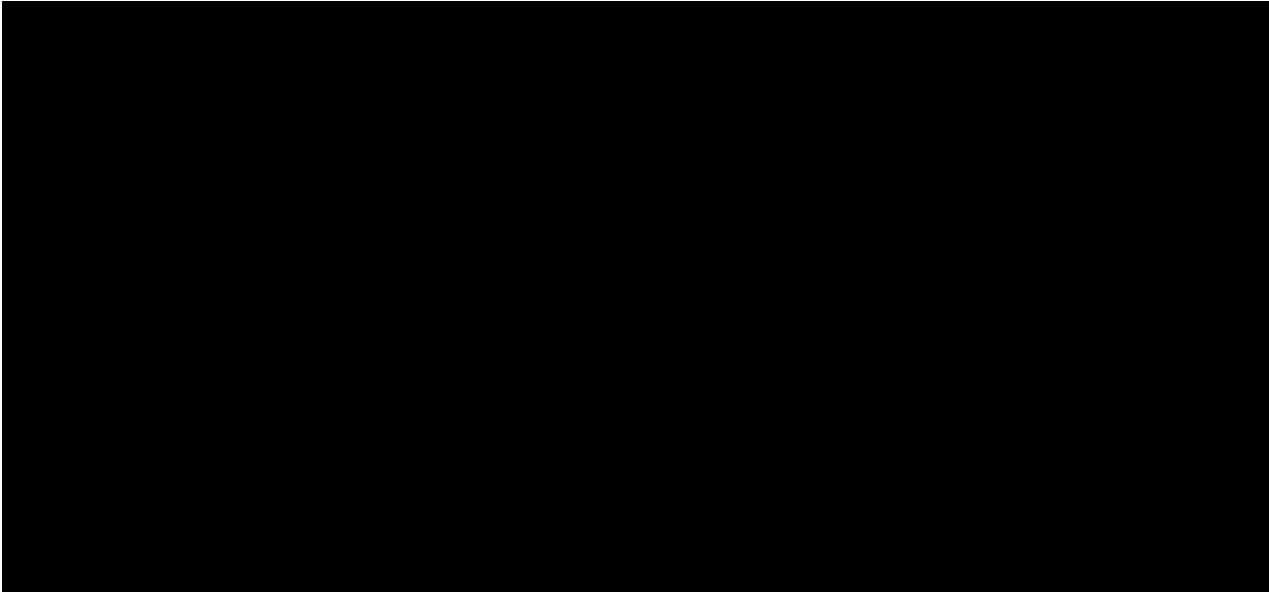
[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

² Bantle, testifying “treatment” includes *harmful* T2D impacts, isn’t credible—and should be disregarded. EX2552, 15:20-16:20; *Elbit Sys. of Am., LLC v. Thales Visionix, Inc.*, 881 F.3d 1354, 1358 (Fed. Cir. 2018) (Board “entitled to weigh credibility”).



Petitioner *recasts*—rather than disputes—the facts. Rep.2-3. Petitioner’s attempts, *e.g.*, to reduce Jensen’s testimony to one-word conclusions (Rep.3-4 (“viable,” “appropriate”)) or dismiss as irrelevant (Rep.3-5) her described mental path are baseless: these are pertinent to how and when she conceived. And Petitioner’s criticism that her last step ( together) didn’t require much time (*see* Rep.3) ignores the law (§103: “Patentability shall not be negated by the manner in which the invention was made”), her scientific analysis, and the massive effort (including the 1821 Trial) making that step possible.

No evidence indicates Jensen “derived” or “reproduced” an *already-conceived invention*. *Cf.* Rep.4 (*citing Solvay S.A. v. Honeywell Int’l*, 622 F.3d 1367, 1376-1379 (Fed. Cir. 2010)). Petitioner *never attempts* to show 

[REDACTED] or anyone else previously conceived the complete invention³ (Rep.2-4,
6); none had, e.g., the [REDACTED] leading to Jensen's conception. Compare,
e.g., [REDACTED]

EX1312 66:4-67:1. Petitioner's evidence (Rep.2-3) shows the opposite:

The mere suggestions “ [REDACTED] (EX1312, 26:15-22) or of **testing** 1.0mg among others ([REDACTED]) are “just a general goal... [they] hope[d] to pursue,” not conception.⁴ *Creative Compounds, LLC v. Starmark Lab ’ys*, 651 F.3d 1303, 1312 (Fed. Cir. 2011); *Dawson v. Dawson*, 710 F.3d 1347, 1353 (Fed Cir. 2013) (“preliminary statement about a possibility... alongside a recommendation for continued work and a [future] ‘report back’... falls short”); *Amgen, Inc. v. Chugai Pharm. Co.*, 927 F.2d 1200, 1206 (Fed. Cir. 1991) (rejecting “simply a wish to know”). Indeed, long after “ [REDACTED]

³ Overcoming the presumption of correct inventorship requires clear and convincing evidence. *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997); *Incyte Corp. v. Concert Pharms., Inc.*, PGR2021-00006, Pap.70, 11-16 (Oct. 11, 2022).

⁴ Nor are they “admi[ssions]” Jensen “did not conceive.” Rep.4.

[REDACTED] remained in flux. Rep.3;

[REDACTED] EX1312, 21:14-22:8, 30:1-

31:19, 37:3-12; *Burroughs Wellcome Co. v. Barr Lab 'ys*, 40 F.3d 1223, 1229 (Fed. Cir. 1994) (“idea... in constant flux... not definite and permanent”).

Petitioner’s “beside[-]the[-]point” hedging about “[w]hether Jensen is a proper inventor” (Rep.8) reflects Petitioner’s misunderstanding of conception. Even crediting Petitioner’s unsupported arguments about someone else **contributing to** Jensen’s invention wouldn’t **negate** Jensen’s conception: that “someone” would be a co-inventor. *E.g., Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1461 (Fed. Cir. 1998) (“alleged... co-inventors must prove their **contribution to the conception**”); *Coleman v. Dines*, 754 F.2d 353, 359 (Fed. Cir. 1985) (conception is “complete performance of the mental part of the inventive act”). Nor could they carry Petitioner’s burden on WO421. *E.g., Incyte*, PGR2021-00006, Pap.70, 11-16 (confirming “presumption of correct inventorship” applies in AIA proceedings).

And Petitioner mistakenly conflates *conception* with *reduction-to-practice*.⁵ Rep.4-5, 8. Phase III testing of Jensen’s selected dose doesn’t mean her mental steps leading to conception (to “[t]hereafter to be applied....,” *REG*, 841 F.3d at 962) were, instead, reducing *someone else’s* conception to practice.

B. Petitioner’s Incorrect Corroboration Standard

Multiple contemporaneous documents—and Flint’s testimony (EX2051, ¶¶4-5)—corroborate Jensen’s invention story, including her medical-director role and responsibilities in PO’s semaglutide project, her analyses regarding 1.0mg, and [REDACTED]. POR.14-16.

Petitioner’s attacks on individual pieces of evidence as pre-dating conception, or purportedly not expressly tying the claimed regimen to Jensen, fail. Rep.5-6. Corroboration “is evaluated under a ‘rule of reason’ analysis [requiring] an evaluation of all pertinent evidence... so that a sound determination of the credibility of the alleged inventor’s story may be reached.” *Ethicon*, 135 F.3d at 1461; *Transweb, LLC v. 3M Innovative Props. Co.*, 812 F.3d 1295, 1302 (Fed. Cir. 2016) (“reject[ing] element-wise attack on corroboration”); *NFC Tech., LLC v. Matal*,

⁵ Reduction to practice happens only after the inventor “appreciate[s]... what [s]he made.” *Dow Chem. Co. v. Astro-Valcour Inc.*, 267 F.3d 1334, 1341 (Fed. Cir. 2001).

871 F.3d 1367, 1372 (Fed. Cir. 2017) (goal to determine credibility). “Corroborating evidence may take many forms” and doesn’t require “corroborat[ing] every [contested] factual issue,” *Ethicon*, 135 F.3d at 1459, 1461, 1464, “an... over-the-shoulder observer,” *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998), or a single explicitly-corroborating document. *NFC*, 871 F.3d at 1372. Indeed, “[circumstantial evidence about the inventive process, alone, may... corroborate.” *Sandt Tech. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1351 (Fed. Cir. 2001). Petitioner’s piecemeal criticisms ignore the rule-of-reason’s holistic framework and voluminous corroborating evidence.

First, Petitioner’s complaint some documents pre-date conception (Rep.5-6 (criticizing [REDACTED])) ignores they confirm Jensen’s investigation into a viable dosing regimen, which she testified led ultimately to her conception. *See, e.g.*, EX2050, ¶¶10-17. [REDACTED], *e.g.*, corroborates Jensen’s testimony on her analysis to form her definite and permanent idea—[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] EX2050, ¶¶18-21. Petitioner never disputes these documents’ contents, which directly evidence Jensen’s inventive process, and strongly corroborate her resulting conception. *E.g., Ethicon*, 135 F.3d at 1461.

Second, Petitioner’s attack on corroborating documents for “not t[ying] the idea of 1.0mg to Jensen” (Rep.6 (criticizing [REDACTED])) ignores they show the claimed dosing regimen *had been conceived by the time of the documents*. Each references Jensen as author, presenter, and/or participant,⁶ and Petitioner never attempts to show any *other* referenced individual conceived. Contrary to Petitioner’s false suggestion about “Jensen admi[ssions]” (Rep.6), Jensen *repeatedly corrected counsel’s misreading of* [REDACTED] [REDACTED].

EX1312, 101:4-20. Together these documents corroborate that, by the time Jensen and her team recommended Jensen’s regimen, her conveyed idea was “definite and permanent” in its “complete and operative” form as “thereafter... applied” in Phase III testing. *REG*, 841 F.3d at 954.

Petitioner’s *NFC* and *Weaver* citations are inapt. *NFC* didn’t rely solely on an inventor-authored data-sheet (*cf.* Rep.6), but *multiple* documents, including a “PCB layout” *not naming the inventor*. *NFC*, 871 F.3d at 1372-73. Here, PO’s evidence all names Jensen. And, unlike here, *Weaver* involved undated photos and a manual only by *other authors*, *without explaining* how it supported the putative

⁶ Petitioner asserts [REDACTED]
[REDACTED]. See EX2050, ¶17.

inventor. *Weaver v. Houchin*, 467 Fed. App'x 878, 881 (Fed. Cir. 2012) (non-precedential).

Finally, Petitioner (Rep.7) ignores [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] EX1312, 104:10-13. Flint never claimed to cite documents “demonstrat[ing] the 1.0mg dose came from Jensen.” *Cf.* Rep.7. Indeed, when pressed to say PO’s exhibits don’t “identif[y Jensen] as the first person to conceive,” Flint explained these documents aren’t the type to do so. *E.g.*, EX1311, 87:5-14, 69:2-70:10. Instead, Flint’s corroborating testimony was based on her recollection of work on the semaglutide team. *E.g.*, EX1311, 77:3-78:1; *cf.* Rep.7.

II. Grounds 1-2 Fail

A. Ground 1

1. WO421’s “Range” Is Five Doses

Petitioner failed to show POSITA would have understood WO421’s “range” as anything other than *the five actual doses NCT657 tested*—which *didn’t include*

1.0 mg.⁷ That some dose(s) **might** work doesn't mean Petitioner's arbitrarily-declared "number" of additional doses within the "range" (and no more) were actually disclosed—or that **any**, let alone **all**, in-"range" doses **would "treat[]"** T2D.

See Sanofi-Synthelabo v. Apotex, Inc., 550 F.3d 1075, 1082-84 (Fed. Cir. 2008) (no anticipation where reference taught 3-member prior art genus: "knowledge... enantiomers **may** be separated is not 'anticipation' of a specific enantiomer that **has not been**"); *Nidec Motor Corp. v. Zhongshan Broad Ocean Motor Co.*, 851 F.3d 1270, 1274 (Fed. Cir. 2017) ("missing limitations [may not be filled in] simply because [POSITA] would immediately envision them").

2. WO421 Doesn't Disclose Just 16 Doses

Even if interpreted without NCT657, WO421 wouldn't anticipate because its range would be "an enormous, and potentially an infinite number" of doses. *Fonterra Co-Operative Grp. Ltd. v. Arla Foods Amba*, IPR2022-00661, Pap.15, 10-11 (Aug. 31, 2022) (recognizing "potentially an infinite, number of such discrete points within the continuous range of 0% to 5%"; "A single, discrete point suggests a difference in how the invention operates at another discrete point [and]

⁷ Petitioner's argument 1.0mg wasn't "**necessarily**.... outside the studied range" because it "could be estimated from the **dose response curve**" (Rep.9) omits that **POSITA didn't have it**. POR.30.

compared to a range disclosed in the cited prior art...’); *see* EX2553, 42:5-43:9 (dosing possible at intervals <0.1mg); EX2552, 17:13-18; POR.23-25.⁸ Petitioner’s attempt to generate a hand-picked selection of 16 that includes 1.0mg (“a nice round number,” per its “expert”) is hindsight-driven rewriting. *Janssen Pharms. Inc. v. Watson Lab’ys, Inc.*, No. 08-cv-5103-SRC, 2012 WL 3990221, at *6-9 (D.N.J., Sept. 11, 2012) (rejecting “creat[ing] hindsight anticipation” by rewriting range to 5mcg increments: other doses are possible, and reference didn’t

⁸ Petitioner **ignores**—and thus can’t distinguish—*Fonterra* (POR.31), where petitioner failed to demonstrate “why... anticipation of a claim requiring a **specific** water content of 3% is supported by a reference teaching a **much broader range**... between 0% and 5%.” *Id.*; *see also* *Regeneron Pharms., Inc. v. Mylan Pharms. Inc.*, 2024 WL 382495, at *47-49 (N.D.W. Va. Jan. 31, 2024) (rejecting “arbitrar[ily] and improperly select[ing] 40 mg/ml” from “five-fold range of 10-50 mg/ml” “encompass[ing] hundreds of discrete concentrations... (like ‘28’ mg/ml, ‘37.2’ mg/ml, and ‘49.35’ mg/ml)”), *74-78 (no anticipation: art disclosed potentially “infinite” number of possible treatment regimes and thus particular claimed regimen wouldn’t be immediately envisaged); *Janssen*, 2012 WL 3990221, at *6-10 (**range** of “.02-0.05 mg” didn’t anticipate **specific** “0.025 mg” **dose**; “Defendants’ ‘narrowing’ effort has no precedent in *Petering*.”).

“*expressly* spell out a definite and limited class”); EX2553, 25:19.⁹ Petitioner cites no precedent narrowing a range as Petitioner argues, particularly *without disclosed results for any dose* (like WO421).

Petitioner (Rep.12) hasn’t and can’t establish POSITA would “at once envisage” 1.0mg.¹⁰ Even if one could properly slice WO421’s “range” into discrete

⁹ Contrary to Petitioner (Rep.13), it *did* contradict the Board (Inst.32) because Bantle *didn’t distinguish “exendin analogues” from “GLP-1 analogues”*—he explicitly identified exenatide as a “GLP-1 analog[.]” EX2018, 54:8-22; POR.23 (citing EX2018-EX2019).

¹⁰ Petitioner’s new construction (Rep.10-11) is late and irrelevant, and its cases inapt. None concocts a discrete number of species/doses within a genus/range. In *Viskase Corporation v. American National Can Company*, application of “standard scientific convention” was *reversed* based on prosecution, and the term was “*about* 0.91”—*not* “0.91.” 261 F.3d 1316, 1322 (Fed. Cir. 2001). Petitioner’s second citation *is to the dissent*. Rep.11. And Petitioner’s “ordinary[-]rounding[-]principles” argument conflates (1) construction and (2) *POSITA’s understanding of WO421*. Only the latter matters. Even if considered, it is belied by the caselaw, and ignores evidence contradicting Petitioner’s assertion that stated dosing

doses different from NCT657's, WO421 doesn't give sufficient information to "at once envisage" 1.0mg as claimed—particularly as it's ***ten times*** WO421's lowest "range" endpoint. *Nidec*, 851 F.3d at 1274; *see Atofina v. Great Lakes Chem. Corp.*, 441 F.3d 991, 999-1000 (Fed. Cir. 2006); *Sanofi-Synthelabo*, 550 F.3d at 1082-84; *Galderma Lab 'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 844-45 (Fed. Cir. 2020) (non-precedential); *cf. UCB, Inc. v. Actavis Lab 'ys UT, Inc.*, 65 F.4th 679, 688-89 (Fed. Cir. 2023) (reversing where court "improperly extend[ed] *Kennametal*" to say prior-art range disclosed a point); POR.26-27 (collecting cases).

Petitioner's attempt to distinguish "957 predicted salts" in *Mylan Pharms v. Merck Sharp & Dohme Corp.*, 50 F.4th 147, 153-54 (Fed. Cir. 2022) is belied by that Court: "[w]e cannot provide a specific number defining a 'limited class'"—and *Mylan* involved a known class, not a range. Further, as here, the art didn't point POSITA toward the claimed species. *Id. In re Petering*, 301 F.2d 676, 681 (C.C.P.A. 1962) confirmed a disclosure not "express[ly] limit[ing] the [group's] size" is insufficient to anticipate—contrasted with disclosures there ***pointing to a limited number of combinations*** within a vast number of options. *See Eli Lilly &*

increments less than tenths-of-a-milligram wouldn't be meaningful to POSITA.

E.g., EX2069, 1; EX2070, 6.

Co. v. Zenith Goldline Pharms., Inc., 471 F.3d 1369, 1375-76 (Fed. Cir. 2006) (explaining *Petering*). None of these cases stand for the **rejected** “proposition that a reference missing a limitation can anticipate a claim if a skilled artisan viewing the reference would ‘at once envisage’ the missing limitation...” *Nidec*, 851 F.3d at 1274 (reversing Board’s anticipation finding and criticizing overly-broad interpretation of *Kennametal, Inc. v. Ingersoll Cutting Tool Co.*, 780 F.3d 1376, 1381 (Fed. Cir. 2015), which focused on whether the “‘number of categories and components disclosed in [the prior-art reference] is so large that the combination... would not be immediately apparent.’”); *see also Eli Lilly & Co. v. Los Angeles Biomedical Res. Inst. at Harbor-UCLA Med. Ctr.*, 849 F.3d 1073, 1074-75 (Fed. Cir. 2017) (rejecting anticipation where defendant argued POSITA would understand “chronic administration” to include “45 days or more”).

3. Petitioner’s Criticality Arguments Fail

Criticality is relevant when a ***claimed range*** overlaps with a ***prior-art range***, and considers whether part(s) of the prior-art range function differently. *OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc.*, 701 F.3d 698, 705-06 (Fed. Cir. 2012). Even if, *arguendo*, a ***range*** could anticipate a ***single point/dose*** (it doesn’t),¹¹ a

¹¹ Petitioner cites no case where a broad numerical range anticipated a single, discrete point (Pet.26-34; Rep.8-15), such that criticality even needs to be considered.

1.0mg dose **would be** part of a critical range within WO421’s broad disclosures. POR.30-35; *OSRAM*, 701 F.3d at 705-06 (describing criticality, vacating anticipation given dispute whether “lamp would operate differently at various points within [disclosed] range”).

Contrary to Petitioner’s assertion, differences in results from practicing the claimed method (here, including efficacy and tolerability) **need not themselves be claimed** to establish criticality.¹² Rep.14. *OSRAM*’s differences in operation—relating to “practicality”/“[e]fficiency”—**weren’t claimed**, but the Court remanded for **criticality** analysis. 701 F.3d at 701, 706. As in *OSRAM*, ’462 consistently distinguishes between results for doses *below* 0.8mg (or 0.7mg (POR.33 & n.18)) and those *above* it, because they treat T2D differently—indeed, certain WO421 doses **don’t** “treat[]” (*e.g.*, 0.1mg provides no statistically-significant HbA1c impact, and 0.1mg/0.2mg/0.4mg no statistically-significant weight-loss). EX1001, Figs.1-5, 1:31-4:24 (“**at least 0.7 mg**” weekly); EX2010, ¶¶241-253; POR.30-35.

¹² Bantle’s and Jusko’s criticality analysis should be ignored because they wrongly assumed “to be critical, the patent would need to require a specific degree of efficacy or tolerability.” EX2552, 11:14-13:13, 42:14-43:2, 58:3-59:9; EX2553, 11:11-21, 18:19-20:22, 23:4-24:5.

Similarly, *Atofina*, *Ineos*, and *Genentech* don't require claiming the results' differences, or that part of the prior-art range be inoperable, for a range subset to be critical. *Cf.* Rep.14-15. *Atofina* simply relies on "the considerable difference between the claimed [and prior art] range[s]." 441 F.3d at 999; POR.29-30. And *Ineos USA LLC v. Berry Plastics Corp.*, describing *Atofina*, ***doesn't require*** claiming results or inoperability within the disclosed range. 783 F.3d 865, 869 (Fed. Cir. 2015). *Ineos* considered whether POSITA "would have expected... synthesis... to operate ***differently, or not all***, outside [the claimed] range": "[i]f the prior art discloses its own range... [that] is ***only anticipatory if it describes the claimed range with sufficient specificity*** such that a reasonable fact finder could conclude that ***there is no reasonable difference in how the invention operates over the ranges.***" *Id.* *Genentech, Inc. v. Hospira, Inc.* also doesn't require inoperability or claiming results—and Petitioner's quote (Rep.14-15) is about why *Atofina's* claimed range was critical. 946 F.3d 1333, 1338 (Fed. Cir. 2020).

Petitioner ***concedes there was no prior-art semaglutide data to provide any guidance about how any portion of the range behaved.*** Rep.25. And Petitioner admits POSITA ***would have expected differences*** (Pet.41; EX2019, 103:21-105:1; EX2552, 42:14-43:2, 45:6-47:2; EX2553, 41:3-15; EX1300, ¶¶51-52; EX1301, ¶¶210-215), and in any event the 0.1mg semaglutide dose, for example, was inoperable (*supra*, pp.15-16). *See* POR.30-35; EX1001, Figs.1-5, 1:31-4:24, 23:3-14.

Contrary to Petitioner’s mischaracterizations (Rep.15), Dr. Rosenstock explained the data demonstrates *meaningful differences across the range*. EX2010, ¶¶241-258. WO421’s endpoints certainly encompass “inefficient and impractical” low doses. *OSRAM*, 701 F.3d at 705-06. And ’462 discloses doses *over 0.8mg* are critical to treating T2D, including because of the surprising and unexpected HbA1c and weight loss at those doses. EX1001, Figs.1-5. That semaglutide’s weight loss, tolerability, and efficacy differed (compared to placebo and liraglutide) in the 0.8-1.6mg range confirms criticality. EX2010, §VIII.A.4; POR.30-35; EX2552, 42:14-43:2; 45:6-46:7. It is irrelevant that 1.0mg is not specifically identified as critical *within* that critical sub-“range” (EX2010, ¶¶240-258; *cf.* Rep.14-15): as in *Atofina*, a narrower *range* can be critical.¹³ Moreover, 1.0mg is critical at least for a substantial subset of the T2D population. EX1140, 29:11-30:20, 34:14-35:16 (“start with .25, move to .5 and move to 1 in *virtually everybody*.”); EX2069, 1; EX2300, ¶¶81-87.

¹³ Bantle’s and Jusko’s criticality opinions incorrectly assume 1.0mg must be different from “*all other doses*” in the prior-art range. EX2552, 41:13-43:2, 58:3-59:9; EX2553, 18:19-19:2.

Even if, *arguendo* (Rep.13-14), criticality required results be claimed, Petitioner's experts *concede the claimed "method of treating" requires expected efficacy and tolerability*. *Supra* pp.1-2; POR.30-35.

4. Petitioner's Ground 1 Claim 3 Argument Additionally Fails

Petitioner's Reply theory (Rep.16) confirms the Petition's deficiencies in arguing claim 3's solution was *inherently disclosed*. Pet.35-36 ("*necessarily* a solution"); EX1005, ¶200; EX1003, ¶272. While Petitioner now improperly argues "WO421 *expressly discloses*... 'injectable solutions,'" relying on a *previously-uncited* portion of WO421 (Rep.16 (citing Ex1011, 40:23-26); Pet.35-36 (40:23-26 *not cited*)), Petitioner's new theory is prohibited.¹⁴ And the Petition's inherency theory fails even with this new WO421 quote, from which Petitioner *omits* a key

¹⁴ *E.g., Intelligent Bio-Sys. v. Illumina Cambridge Ltd.*, 821 F.3d 1362, 1369-70 (Fed. Cir. 2016) (affirming rejection of new theory referencing new evidence); *Wassica Finance GmbH v. Cont'l Auto. Sys., Inc.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017) ("Rather than explaining *how its original petition was correct*, Continental[] [argued] *entirely new theory of prima facie obviousness....*"); *In re NuVasive, Inc.*, 841 F.3d 966, 971-73 (Fed. Cir. 2016) (vacating/remanding where Board relied on prior-art figure first argued in reply); *Dell v. Accelaron, LLC*, IPR2013-00440, Pap.49, 13 (Aug. 22, 2016).

portion confirming the Petition’s relied-on subcutaneous injection is ***not necessarily*** a solution, but instead ***may be a suspension***: “Injectable formulations of the GLP-1 receptor agonists of this invention may be... injectable solutions ***or suspensions***.” EX1011, 39:20-26. Petitioner also doesn’t dispute EX2004 refers to injectable *suspensions*, but argues EX2004’s “large needle” was “***inappropriate for humans***.” Rep.16. Nonsense: Bydureon’s suspension was FDA-approved ***for humans***. EX2010, ¶418; EX2420, 1.¹⁵

B. Ground 2

Petitioner’s Ground 2 Reply incorporating its Ground 1 arguments (Rep.17-18) fails for the same reasons. Petitioner’s additional arguments relying on supposed POSITA inferences ***based on disclosures of other GLP-1s treating T2D*** (Rep.18-19) confirm Lovshin doesn’t anticipate. *Net MoneyIN, Inc. v. VeriSign, Inc.*, 545 F.3d 1359, 1369 (Fed. Cir. 2008); POR.36-40. Lovshin’s reference to “NN9535” “as an incretin treatment” (Rep.18-19) doesn’t disclose ***treating*** T2D with the required expectation of efficacy and tolerability (*supra* pp.1-2), let alone at any particular dose. “NN9535” was, instead, “under active clinical investigation.” EX1012, 5; EX2556, 70:11-73:7; *Slayback Pharma LLC v. Eye Therapies*,

¹⁵ Petitioner’s indefiniteness arguments (Rep.16-17) aren’t cognizable in an IPR.

LLC, IPR2022-00142, Pap.77, 35 (May 15, 2023) (no anticipation where art didn't disclose required intent to treat).¹⁶

III. Grounds 3-5 Fail

Petitioner again relies on the inapt presumption in *Galderma Laboratories v. Tolmar, Inc.*, 737 F.3d 731, 737-738 (Fed. Cir. 2012): but PO's claimed "1.0 mg" dose "is a single, discrete *point*," not a *range*—and not just "somewhat narrower" than the prior-art range. *Fonterra*, IPR2022-00661, Pap.15, 15. And, unlike here, *Galderma*'s prior art demonstrated its range was "effective... and well tolerated." 737 F.3d at 734, 736. Even if *Galderma*'s "presumption" applied, it's rebutted "by showing criticality" or objective indicia—PO established both. *Genentech*, 946 F.3d at 1341; §§II.A.3, III.D; see POR§§VII.A.1.c, VIII.F. Petitioner's remaining obviousness arguments also fail, as discussed below.

A. Motivation to Combine

Petitioner reasserts that, "[b]ecause clinical trials were underway... safety and efficacy" can be *assumed*, and all that remained was optimizing "within that range." Rep.20. But Petitioner provides no cases establishing such "safety and efficacy" assumptions (Rep.20), and no scientific, reasoned basis—absent

¹⁶ Bantle's understanding of the preamble's construction was incorrect and inconsistent with *Jusko*. *Infra*, §IV.

hindsight—for selecting 1.0mg. Rep.20-24; *see also* POR.41-45; EX2556, 81:11-83:4, 139:1-140:7; §42.65(a); *infra* §IV.

Petitioner again argues selecting 1.0mg didn’t involve “modif[y]ing” its references (*but see* POR.41-44), and instead was merely “routine **optimization**.”

Rep.20. But Petitioner’s experts had no reasoned basis to conclude any “range” would be understood as limited to 16 doses (§II.A.2),¹⁷ and ***never determined whether 1.0mg is “optimal”*** (despite contrary suggestions in their declarations). Compare EX2552, 46:18-47:2; EX2553, 25:6-27:10, 28:10-29:18 with EX1300, ¶266; EX1301, ¶267; Rep.23-24; *see infra* pp.24-25; POR.41-44. Petitioner misapplies *In re Ethicon, Inc.* to argue “routine optimization” doesn’t require the claimed value be optimal (Rep.23), but ignores the ratio there “achieves ***the optimal combination***....” 844 F.3d 1344, 1350-51 (Fed. Cir. 2017); *see also In re Peterson*, 315 F.3d 1325, 1330 (Fed. Cir. 2003). And *SNF S.A. v. Solenis*

¹⁷ This squares with *Alcon Research Limited v. Watson Laboratories*, where “the number of alternatives was neither ‘finite’ nor ‘small’” because there was “no teaching to select the ternary system from...[the] number of possibilities....” 2018 WL 1115090, at *22 (D. Del. Mar. 1, 2018); *cf.* Rep.22. And, like in *Alcon, Inc. v. Teva Pharmaceuticals USA*, there were (at minimum) thousands of options in the prior-art range. 664 F. Supp. 2d 443, 461 (D. Del. 2009).

Technologies, L.P., IPR2020-01730, Pap.10, 16-19 (Apr. 22, 2021) shows a claimed optimum is required: the Board analyzed whether optimizing would actually **lead to the claimed value**, not whether POSITA would **try** it. *Id.* Petitioner also ignores how other variables (like titration and dosing frequency, both impacting tolerability (EX2010, ¶¶136-141, 284)), would complicate its optimization rationale. Pet.39-42. And even if the law didn't require the claimed value be optimal, **Petitioner's argued-for motivation does**: Petitioner's argument was **to optimize to 1.0mg**. Pet.44; *Intelligent Bio-Sys.*, 821 F.3d at 1367-69 (claims not obvious where argued combination not expected to provide solution that supposedly motivated combining).

Petitioner further errs in relying on cases that **aren't** "routine optimization" cases to argue "routine optimization" doesn't require the claimed value be optimum. Rep.23-24; *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994) (whether **suboptimal** combination **teaches away**); *Novartis Pharms. Corp. v. West-Ward Pharms. Int'l Ltd.*, 923 F.3d 1051, 1059-60 (Fed. Cir. 2019) (saying nothing about optimization); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Janssen Pharms. Inc. v. Teva Pharms. USA, Inc.*, 97 F.4th 915, 926 (Fed. Cir. 2024).

Finally, while "[o]ptimization and criticality are... not the same," Petitioner is incorrect that 1.0mg is "not critical" "[e]ven if [it] were optimal." Rep.22. Not every dose in the disclosed range "treat[s]" T2D. *Supra* pp.1-2; POR.30-35. And

while “T2D can be treated with both lower and higher doses,” that doesn’t preclude a critical range within WO421’s/Lovshin’s “range” that includes 1.0mg—*e.g.*, doses over 0.8mg. §II.A.3; POR.30-35.

B. REOS

Petitioner’s hindsight-driven arguments don’t cite *data* pointing to any purported “sweet spot,” and don’t show assuming weekly semaglutide dosing from daily liraglutide dosing was reasonable. *See* Rep.26-27; POR.2-4, 64-66; *Salix Pharms., Ltd. v. Norwich Pharms. Inc.*, 98 F.4th 1056, 1062-63 (Fed. Cir. 2024) (“we are hesitant to conclude... a Phase II clinical trial plan...provides [REOS for] a dosage... not included within the... trial”; relying on *separate reference’s* results and explicit statements about optimal dosing for REOS); *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1346-47 (Fed. Cir. 2021); *Novartis*, 923 F.3d at 1060-61.

First, Petitioner argues “lack of data” “only meant POSAs would not have known *how* effective any dose was.” Rep.24-25 (emph.orig.). But the lack of *any* data at *any* dose is relevant to REOS. *Eli Lilly*, 8 F.4th at 1346-47 (affirming non-obviousness where “Board observed... both [references] lacked efficacy data,” which, while not required, evidenced lack of REOS). Petitioner identified no teaching showing the prior-art range was an “established effective range,” and argues optimization of two *different* ranges, 0.1mg-1.2mg/1.6mg (*Mylan Pharms.*

Inc. v. Biogen MA Inc., IPR2018-01403, Pap.98, 16-17 (Feb. 5, 2020); Rep.26; EX2556, 81:11-83:4, 139:1-140:7; EX2552, 36:16-20; §42.65(a))—and it ***was not known if efficacy was dose-dependent within either range*** (POR.48-49) or whether the optimal dose was within either (EX2552, 46:18-47:2, 53:1-7).

Second, Petitioner asserts the “trials’ dosing schemes... suggested a sweet spot... between... 0.8-1.6mg or 0.8-1.2mg,” but doesn’t sufficiently support its (or its experts’) conclusory assertions with evidence. Rep.26.¹⁸ Phase II trials routinely fail, which Petitioner fails to rebut with evidence—trying to gloss over that, despite reaching Phase III, taspoglutide ***as administered in Phase III trials was not safe and effective***. Rep.28-29. Moreover, not enough was known to rely on “similarities between semaglutide and liraglutide.” Rep.27; POR.63-66; EX2010, ¶¶119-122, 358-359, 393. Spiegel, for example, admitted insufficient evidence existed to know whether semaglutide would work like other GLP-1 agonists

¹⁸ This assumption, based on NCT773’s top dose being 1.2mg (vs. 1.6mg) in healthy subjects, ignores POSITA’s understanding of potential *Japanese*-population-specific rationales. EX2010, ¶¶99-102, 409-412; EX1014, 8. Even if guesses were made about the tested doses’ significance, titration for upper doses suggests tolerability concerns there. *See* EX1300, ¶¶304-306 (“could be considered more of a factor”).

(including liraglutide), and at what doses. EX2556, 81:11-83:4, 139:1-140:7; POR.44-45. And, *no prior art evidenced a basis to assume the dose-response curves were even similar*; which semaglutide and liraglutide doses would behave similarly; or whether 1.0mg semaglutide would have been a claimed “treatment” based on its curve. EX2554, 105:7-106:19 (unaware of any “known data for any dose of semaglutide” as of 2012); EX2553, 35:16-36:19 (dose-response curve opinions depend on unsupported assumption “*nearly all [drugs]* have a sigmoidal dose-response curve,” and admitting doses wouldn’t be the same); Rep.28; POR.63; EX2010, ¶¶357-358. For example, Bantle unreasonably assumed any GLP-1 analog with 8 overlapping essential residues would work at all doses within any range tested in a trial. EX1300, ¶¶298-300, 317. But Petitioner plainly fails to account for structural *differences* impacting efficacy and tolerability.¹⁹ EX2010, ¶148; EX2553, 38:3-39:13, 40:17-41:15; EX2556, 80:12-81:10; EX2552 40:16-41:9, 57:1-5.

Petitioner’s spin on semaglutide being “on hold” or “postponed” also fails. Rep.29-30. PO’s delaying further semaglutide trials for over a year is not a basis

¹⁹ Dr. Bantle contradicted his declaration opinion at deposition, but gave no reasoned basis for knowing when or how a GLP-1 agonist sharing these amino acids would be expected to behave like liraglutide. EX2552, 56:17-57:5.

to conclude success. EX2556, 106:22-108:2; EX2552, 22:8-16. And even if considered, Petitioner’s late reliance on a report of *semaglutide*’s clinical efficacy and safety being “broadly in line with liraglutide” (*see* Rep.25, 30) says nothing about *which dose(s)* worked or were tolerable or aligned with which *liraglutide* doses. *See* EX2552, 29:4-16; 33:5-15.

Finally, Petitioner asserts “clinical trials, although expensive and time-consuming, *would have been routine*[.]” Rep.30. But Petitioner identifies no case supporting its argument clinical trials are “routine experimentation”—particularly here, which would involve testing a molecule with *no established effective range*—and doesn’t distinguish *CSL Behring LLC v. Bioverativ Therapeutics Inc.*, IPR2018-01345, Pap.10, 21 (Jan. 16, 2019). POR.51.

C. Additional Ground 4 and 5 Failures

Ground 4 additionally fails because Petitioner identifies no data in Lovshin or elsewhere showing 1.0mg semaglutide could “treat” T2D—thus, Lovshin doesn’t disclose the preamble (an additional reason no presumption applies).

§II.B.

Ground 5 similarly fails with respect to NCT657 and NCT773. §II.B. Further, Petitioner mischaracterizes PO’s arguments about NCT773’s trial concerning Japanese subjects. Rep.33. PO does *not* argue Petitioner’s theory is limited to that population, but that Petitioner’s reliance on any NCT773 *change in dose* from

1.6mg to 1.2mg is flawed: that change would have been understood as accounting for known sensitivities in that population, not zeroing in on a sweet spot. POR.77-78; n.18; *see also* EX2552, 28:11-29:3.

D. Petitioner’s Attacks on Objective Evidence Fail

1. Nexus

Petitioner errs in arguing against a nexus presumption. 1.0mg Ozempic® is “essentially the claimed invention.” *Fox Factory, Inc. v. SRAM, LLC*, 944 F.3d 1366, 1373 (Fed. Cir. 2019). Ozempic®’s label identifies 1.0mg as a maintenance dose for treating T2D (EX2069, §§2.2, 3; EX2054 ¶44), and there is no real dispute 1.0mg Ozempic® embodies the Claims.

Instead, Petitioner disputes coextensiveness because of PO’s weight-reduction patent (which does not claim treating T2D), and a now-pending *application* concerning cardiovascular outcomes in patients with T2D and chronic renal impairment (though Petitioner cites no caselaw finding an *application* relevant to nexus), both of which are used in different populations. Rep.34-36; EX2002. But relying on a feature for unexpected results or praise is not “describ[ing] unclaimed features... as critical.” *Cf.* Rep.34-35. And evidence that “products embody the full scope of the claimed invention” supports a nexus presumption even when unclaimed features are present. *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1419 (Fed. Cir. 2022). Although important, these are not “features”

that “materially impact[] the product’s functionality,” such that the nexus presumption shouldn’t apply. Rep.34-35; *see Fox Factory*, 944 F.3d at 1375.

Moreover, even without the presumption, PO’s objective evidence “is the direct result of the unique characteristics of the claimed invention[.]” *Id.* at 1373-74.

Petitioner never meaningfully refutes this. Instead, it argues all objective evidence must be tied solely to the dosing because once-weekly semaglutide to treat T2D was in the prior art. *See* Rep.36-37. Even if true (it’s not), this would incorrectly “***mean that nexus could never exist where the claimed invention is a unique combination of known elements from the prior art.***” *Chemours Co. FC, LLC v. Daikin Indus., Ltd.*, 4 F.4th 1370, 1378 (Fed. Cir. 2021).

2. Commercial Success

Contrary to Petitioner’s assertions (Rep.36-37), PO confined its analysis to **1.0mg** Ozempic® sales and prescriptions (*e.g.*, EX2300 ¶¶7, 81-87), then analyzed any detractors from that success. *See id.* ¶¶88-93, 97-120. Petitioner’s attacks fail,²⁰ and its expert, McDuff, concedes Ozempic® “earned significant sales”

²⁰ McDuff includes a “product conversion” argument ***never discussed in Petitioner’s Reply***. *E.g.*, EX1308 ¶¶ 59-64. This is waived, but also undermined by McDuff’s deposition testimony. EX2555, 53:11-54:21 (discussing EX2314, 9).

(EX2555 (8:20-9:14)) and—in striking understatement—has enjoyed “a *certain amount* of product success” (although McDuff declined to explain what he means). *Id.* (9:15-11:3); *see also* EX1308 ¶18; EX2556, 106:22-110:6.

Petitioner’s expert used the wrong framework. McDuff contends PO should have considered an “analysis of profits, costs, or risk-adjusted returns,” quoting *Acorda Therapeutics, Inc. v. Roxane Laboratories, Inc.*, 903 F.3d 1310, 1338-39 (Fed. Cir. 2018). EX1308, ¶21 & n.30. But McDuff *cuts from Acorda, with ellipses*, that these recited factors are *not* for analyzing commercial success *generally*, but for possible *blocking-patent* disincentives. *See Acorda*, 903 F.3d at 1338. And as discussed below, McDuff incorrectly analyzed blocking patents.

Nexus for commercial success. While Petitioner complains PO did not properly account for other patents (Rep.36-37), *McDuff*’s opinions about patents covering the injector device (*see* EX1308 ¶¶33-34, 44) relied on explanations from *technical expert, Spiegel* (e.g., *id.*, ¶33). But *Spiegel* confirmed those patents “relate to *devices* and so are not relevant here.” EX1302 ¶49 n.5.

Off-label prescriptions. McDuff principally cites non-peer-reviewed *news-paper articles* (EX1308, ¶¶53-54) and an underlying report purportedly evaluating

And Petitioner never challenged PO’s pricing strategy evidence. *See* EX2300, ¶¶113-16.

prescription increases in patients with “a history of ***overweight, obesity, and other hyperalimentation.***” *Id.* ¶53 (citing EX1184, 43). But this report ***never states these patients didn’t have T2D***, undercutting Petitioner’s off-label argument. *E.g.*, EX2555, 29:21-30:6, 31:6-18. While Petitioner’s ***expert*** didn’t know what percentage of T2D patients suffer from these listed conditions (*id.*, 28:7-10), the ***evidence*** (which McDuff cited) shows [REDACTED] ***of T2D patients*** are overweight or obese. EX2308, 3.

McDuff also relied on two exhibits to derive off-label usage figures: a ***blog post*** with a ***bar chart*** allegedly showing off-label usage with no stated numbers (EX1172), and a “***report***” from “***TrackDrugs.com.***” EX1185. But ***McDuff couldn’t explain*** how the blog could reliably provide the figures he used. EX2555, 36:12-38:1. And ***McDuff never looked at the underlying data***, whose ***only source was “TrackDrugs.com”***—***McDuff had no idea*** who supported that site, ***he couldn’t recall using it before***, and it ***lists only the report McDuff used.*** *Id.*, 34:4-10, 39:11-41:22; 44:22-46:5. And while Petitioner complains (Rep.36-37) about *PO*’s supposed failure to separate commercial success by dose (*cf.* EX2300, ¶¶80, 85-93), McDuff also didn’t break down any alleged off-label usage into ***specific Ozempic® doses***, claiming “[i]t wasn’t necessary.” EX2555, 42:12-43:8, 44:9-17.

Advertising and marketing. While Petitioner’s Reply complains of an “advertising campaign” (Rep.36), Petitioner’s expert ***agreed*** “the promotion to sales

ratio relative to other drugs at similar stages in their life cycle ***does not detract from the conclusion of commercial success.*** EX2555, 59:17-60:2. And Petitioner's cited evidence explains "***a significant advertising budget does not in itself rebut the presumption that the commercial success...***," and confirms a low "ratio of promotional spending to sales" ***supports*** commercial success. EX1180, 9, 11 n.9.

Blocking patents. The "blocking" effect of PO's other patents is minimal. POR.82-83; EX2300, ¶¶117-20. Petitioner offers no analysis showing a mere ***application*** would have diminished economic incentive to develop the claimed invention, and ***cites no case*** treating an ***application*** as a "blocking patent." See Rep.38-39. For good reason: "***claims of a patent*** define the invention"—not pending claims, which may not issue. *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005); EX2555, 66:1-12 (testifying likelihood '343 application would actually ***issue*** was "***not necessary*** for [his] opinions"), 63:21-64:5, 66:13-20, 67:17-19; EX2554, 122:17-123:11 ("claims may change"); cf. *Acorda*, 903 F.3d at 1338 (related likelihood of claim viability—"whether the blocking patent can be successfully challenged"—is "relevant" factor to be considered). The caselaw explains "[a] blocking patent is ***one that is in place*** before the claimed invention," *Chemours*, 4 F.4th at 1379 (citing *Acorda*, 903 F.3d at 1337), and the application leading to PO's '343 didn't include semaglutide-specific claims. EX1015, 65-76.

PO properly confined *its* blocking-*patent* analysis to the dates the patents *issued*. Petitioner’s citation of another PO patent covering GLP-1 compound formulations broadly—8,114,833—fares even worse, given *others were clearly developing GLP-1 formulations even after ’833’s 2012 issuance*. E.g., EX2445; EX2455; EX2475; EX2555, 62:4-21. And 9,764,003 (Rep.35) *issued even later (2017)*. EX2002.

Finally, Petitioner’s expert points to FDA new-chemical-entity exclusivity as evidence of “blocking” (although Petitioner’s Reply does not). See EX1308 ¶¶ 86-88. But FDA exclusivity was granted *five years after* ’462’s latest priority date (EX2555, 68:6-12, 69:22-70:10), and McDuff’s position would mean *no new chemical entity* could ever be commercially successful—certainly not the law.

3. Unexpected Results

Petitioner argues PO didn’t compare unexpected results evidence against the closest art, demanding comparisons to “0.8mg semaglutide... or... 1.8mg ...liraglutide” doses. Rep.39-40. But *there was no data at the priority date for 0.8mg semaglutide*, and often no *relevant* data for 1.8mg liraglutide,²¹ as Petitioner’s

²¹ Petitioner’s suggestion PO failed to compare 1.8 mg liraglutide is facially incorrect. POR.33, 84-85, 88. For example, PO’s unexpected kidney results evidence

experts admitted. EX2557, 22:13-17, 26:17-17:4, 20:3-8; EX2554, 105:7-106:2.

Indeed, Petitioner’s cardiovascular expert published articles comparing GLP-1s *to DPP-4 inhibitors*, underscoring the need to compare against what prior-art data *actually existed*. See, e.g., EX1246, 1-2. And while *post-invention data* may prove *unexpected results*, the question of *what POSITA would have found surprising* is measured *at the time of invention*. See *Forest Lab ’ys., LLC v. Sigmapharm Lab ’ys, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019). Thus, PO’s experts properly compared 1.0mg semaglutide to the closest data *that existed*.

Petitioner also complains of *differences in degree* versus *differences in kind*. Rep.40-42. But Petitioner improperly assumes *all* differences in percentages are merely differences in degree. E.g., *Padagis Israel Pharms. Ltd. v. Bausch Health Ireland Ltd.*, IPR2023-01114, Pap.18, 22-23 (Jan. 12, 2024) (denying institution, rejecting “conclusory and unpersuasive” argument that results including significant improvement percentages—e.g., “31.8% more effective,” “90.3% less

for 1.0mg once-weekly semaglutide in T2D patients was compared against 0.5mg once-weekly semaglutide and 1.8mg daily liraglutide. See EX2015, 8; POR.85.

Spiegel also admitted he was aware of no head-to-head trials of 1.0mg semaglutide against 1.8mg liraglutide and, even if there were, does not believe liraglutide would be comparable to semaglutide. EX2556, 129:10-132:1.

irritating”—“merely represent a difference in degree, not... kind”). “There is no specific fold-difference that defines what may, or may not, support a finding of nonobviousness.” *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 964 (Fed. Cir. 2023). The question of where to “draw [the] line between difference in degree...and a difference in kind” is a “fact-specific” inquiry. *Id.* PO’s experts and other evidence confirm the differences resulting from ’462’s claimed dose were differences in kind. *E.g.*, POR.83-87; EX2054, ¶¶61-83; EX2055, ¶¶34-44; EX2011, ¶¶44-63; EX1001, Fig.5 (30.8% greater weight loss in 0.8mg semaglutide (3.4kg) than 1.8mg liraglutide (2.6kg)); EX2082, 1, 6-7 (comparing 1.0mg semaglutide/1.2mg liraglutide at week 30, 211% more patients hit 5% weight loss (56%/18%), 375% more patients hit 10% weight loss (19%/4%), 205% greater average weight loss (5.8kg/1.9kg), and 70% greater reduction in HbA1c for semaglutide (1.7/1.0)). And it is Petitioner’s experts—not PO’s (*cf.* Rep.40)—who failed to understand this legal principle. *See* EX2557, 27:18-29:7; EX2554, 118:6-119:4; EX2556, 41:22-44:2. Petitioner also misleadingly quotes the law. Although “superior efficacy” may not diminish a proven reasonable expectation of success, Rep.40-41 (quoting *UCB*, 65 F.4th at 693), *UCB* doesn’t eliminate superior efficacy as an unexpected result.

While Petitioner mistakenly criticizes “PO’s kidney expert’s declaration [as] riddled with flaws” (Rep.41; *supra* §III.D.1; EX2011, ¶¶32-35, 44-63; n.21),

Petitioner's kidney expert, Coca, admittedly misquoted, mischaracterized, and overstated the articles he (Coca) relied on. While, *e.g.*, Coca's declaration **purports to quote EX1149** as support (EX2554, 62:18-65:2; EX1306, ¶79) **his manufactured quote doesn't exist and doesn't support him**: its conclusions were documented "in **healthy male volunteers**"—a far cry from Coca's falsely-"quoted" conclusion about "patients who suffered from [T2D]." EX1149, 6; EX2554, 66:9-72:13. And Coca repeatedly overstated conclusions to argue kidney-protective effects were certain or expected, when in reality his cited articles were (1) **early hypotheses** based on soft endpoints in **rodent** studies, (2) studies in small groups of **healthy** volunteers (which Coca failed to mention) where the authors were "speculat[ing]" or needed their "hypothesis to be confirmed by other studies," also based on soft endpoints, or (3) **safety studies** investigating **concerns about using GLP-1 receptor agonists in patients with kidney issues**. EX2554, 13:12-18 (blood glucose, blood pressure both soft endpoints), 42:10-43:1 (animal studies insufficient²²), 55:5-16 ("demonstrate" v. "indicate"), 59:4-62:17 ("Clearly, long-term studies are needed to settle this issue..."), 72:20-74:10 (omitting authors were "speculat[ing]"), 79:5-22 (omitting "hypothesis needs to be confirmed by other studies"), 85:12-97:7 (neither liraglutide study concluded likely to improve kidney

²² Cf. Rep.32.

outcomes); 146:17-147:11 (still not known why semaglutide kidney-protective). Coca also cast an article by Vollenweider (EX1147) discussing a Yu study, and Yu itself (EX1148), *as two separate studies*, and repeatedly *ignored contrary evidence* in his own cited articles. EX1306, ¶77 (discussing Yu (EX1148)), ¶78 (introducing Vollenweider (EX1147) as “Other studies”); EX2554, 50:7-58:13 (“perhaps in paragraph 78, [‘]other studies[’] would be other *experiments*... [I]t was referring to...Yu”), 62:3-62:17, 77:11-79:22. But even Coca acknowledged as “groundbreaking” a recent FLOW study confirming 1.0mg once-weekly semaglutide’s kidney-protective effects are different *in kind*. EX2554, 10:17-12:22; EX2604, 11 (“1.0 mg [semaglutide] once weekly significantly reduced... *major kidney disease events*...by 24%”). Coca identified no prior art expectation for such *kidney-disease* results, or for a *mortality* reduction—but FLOW established 1.0mg once-weekly semaglutide *reduced the risk of death in T2D patients with CKD from any cause by 20%*. EX2554, 10:17-12:22, 19:19-22, 38:13-39:14; EX2604, 1.

Regarding cardiovascular benefits/injury, the *opinions* of Petitioner’s Schwartzbard about what was and wasn’t known before the priority date *contradict Schwartzbard’s own articles* pre-dating this IPR. Compare EX1304, ¶113 (“*GLP-1 receptor agonists were [not] known or believed to cause cardiovascular injury in diabetic patients*”), ¶113 (“the cardiovascular risk reduction associated with

semaglutide was not unexpected”) with EX2601, 13 (“***HF [heart failure] was an initial concern***”); EX2557, 39:7-12, 40:21-41:14. Schwartzbard wrote ***in 2014*** that: there were “***conflicting findings***” and a “***dearth of data***” regarding GLP-1 agonists and heart failure; “***clinical trials [were] necessary to establish safety***”; and “***[n]ew pharmacological agents are urgently needed.***” EX1246, 4, 6-7. In 2020 he noted “[t]his [heart failure] signal... was not confirmed” in a particular liraglutide trial (EX2601, 13 (“nonsignificant ***increases in...HF***...with liraglutide compared with placebo”)), but that data was not published ***until 2016***—at least four years ***after*** ’462’s priority. EX2601, 13, 19; EX2557, 41:16-42:18. And far from all GLP-1s showing a class-wide effect (Rep.40), Schwartzbard wrote in 2018 that then-upcoming trials would “***help clarify whether the CV benefit demonstrated by GLP-1 RA agents is a class effect... or a drug-specific effect only seen with liraglutide and semaglutide.***” EX2602, 10; EX2557, 51:19-52:12, 56:6-57:9.

4. Long-Felt Need

Petitioner’s arguments do not meaningfully rebut PO’s evidence (*e.g.*, POR.87-88), and, as explained (§IV.D.2), Petitioner’s blocking-patent analysis is fundamentally flawed. Spiegel criticizing Goland’s reliance on her treating physician experience (EX1302, ¶212) simply underscores ***Spiegel hasn’t “had direct responsibility for treating patient[s]” since 1976.*** EX2556, 30:8-11, 37:20-39:17.

5. Industry Praise

1.0mg Ozempic[®] has been extensively praised in peer-reviewed scientific articles for treating T2D. PO's employees being among their authors doesn't render these the "bare journal citations and self-referential commendation" *Bayer* criticized. *See* Rep.43. Their ***collected, peer-reviewed, and published data*** isn't irrelevant just because PO was involved. *Compare, e.g.,* Rep.43, with EX2554, 10:17-12:22, 128:8-130:5 (Coca admitting "***groundbreaking*** clinical [FLOW] trial" (EX2604) by "respected scientist[s]" "pertinent to [his] clinical practice and... research").

And Petitioner is wrong that there was no praise regarding cardiovascular risks. Rep.43. Petitioner's Schwartzbard wrote in 2018 there had been a "paradigm shift" that may be "a ***drug-specific effect only seen with liraglutide and semaglutide.***" EX2602, 1, 10; EX2557, 51:19-52:12, 52:16-53:11, 56:6-57:9.

6. Skepticism

Petitioner's arguments don't meaningfully rebut PO's record evidence. POR.90.

IV. Petitioner's Experts' Opinions Should Be Given Little To No Weight And Uncited Paragraphs Ignored

Petitioner's experts' opinions about what POSITA would have known or assumed should be given little to no weight for lacking a scientific reasoned basis for their opinions, and for providing incomplete and contradictory analyses. *E.g.,*

supra pp.1-2 & n.2, 15 n.12, 17 n.13, 20 n.16, 25 & n.19, §III.D.2-3; EX2552, 22:8-16 (can't speak to Novo's intent); 28:11-29:3, 33:19-34:14, 36:16-20; EX2553, 25:6-20, 35:16-36:9; *see also* POR.29, 41 n.22, 49-50 & n.27, 54-57 & n.29. Bantle's and Jusko's opinions almost entirely duplicate one another (*compare, e.g.*, EX1300, §§VI.D, VII.A-G *with* EX1301, §§VII-VIII; *see* EX2552, 9:7-12; *see also* EX1003, §§VIII.A-E, IX *with* EX1005, §§VIII.A-E, IX; POR.n.3), but tellingly they **contradicted each other** at deposition (*e.g., compare* EX2552, 15:20-16:20 (treatment even if it "makes a condition worse") *with* EX2553, 12:20-13:15, 14:7-15:4, 41:3-15 (treating requires tolerability and clinically meaningful efficacy)).²³—confirming Petitioner's improper attempt to bank "backup" experts failed, and their testimony should receive no weight. Further, other than to show deficiencies and inconsistencies with deposition testimony (§III.D.2-3), again confirming Petitioner's experts should be given little to no weight (n.2), the numerous uncited paragraphs of Petitioner's Reply expert declarations shouldn't be considered. *One World Techs., Inc. v. Chamberlain Grp., Inc.*, IPR2017-00214, Pap.31, 29 n.10 (May 15, 2018) (uncited declaration paragraphs given "little weight"); *see* 42.104(b)(5).

²³ Bantle's testimony about efficacy expectations should be ignored given his misunderstanding of "treating." *Supra* pp.1-2 & n.2.

V. Conclusion

Petitioner failed its burden, and '462's patentability should be confirmed.

/J. Steven Baughman/

J. Steven Baughman (Reg. No. 47,414)

Dated: August 5, 2024

CERTIFICATE OF WORD COUNT

The undersigned certifies that the foregoing PATENT OWNER'S SUR-REPLY complies with the type-volume limitation the Board's January 9, 2024 Order (Pap.27). According to the word-processing system's word count, the brief contains 7,591 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a)(1).

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S SUR-
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