



Oral Argument

*Mylan Pharmaceuticals Inc., Dr. Reddy's Laboratories, Inc.,
Dr. Reddy's Laboratories, Ltd., Sun Pharmaceutical Industries
Ltd., and Sun Pharmaceutical Industries, Inc.*

v.

Novo Nordisk A/S

IPR2023-00724*

Inter Partes Review of U.S. Patent No. 10,335,462

Patent Trial and Appeal Board
United States Patent and Trademark Office
August 27, 2024

*IPR2024-00009 & IPR2024-00107 have been joined with this proceeding.

Table of Abbreviations

'462 Patent	EX1001, U.S. Patent No. 10,335,462
Pet.	Paper 1, Petition for <i>Inter Partes</i> Review
Inst.	Paper 10, Decision Granting Institution of <i>Inter Partes</i> Review
POR.	Paper 29, Patent Owner's Response
Rep.	Paper 53, Petitioner's Reply to Patent Owner's Response
SurRep.	Paper 73, Patent Owner's Sur-Reply
T2D	Type 2 Diabetes

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

Illustrative '462 Claims

1. A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.
2. The method according to claim 1, wherein the semaglutide is administered by parenteral administration.
3. The method according to claim 2, wherein the solution is administered by subcutaneous injection.

EX1001 ('462 Patent), Cl.1, Cl.2, Cl.3.

Table of Contents

Claim Construction..... 5

Petitioner’s References 7

Grounds 1 and 3: The ’462 Patent Antedates WO421 19

Ground 5: The ’462 Patent Antedates NCT773 66

Petitioner’s Grounds 1-2 Fail 68

Petitioner’s Grounds 3-5 Fail 114

Objective Indicia Support the Non-Obviousness of the ’462 Patent..... 144

Petitioner’s Experts Should Be Given Little To No Weight 212

Claim Construction

Construction of “A method for treating Type 2 Diabetes”

- The Parties agree the preamble is limiting.
Pet.14-15; POR.10-11
- The Parties also agree no *particular* degree of efficacy (such as a particular level of reduction in HbA_{1c}) is required.
Pet.14-15; POR.10-11
- Petitioner explains the preamble would be understood to require administering semaglutide “to alleviate or reduce symptoms and complications associated with type 2 diabetes or otherwise manage the disease.”
Pet.15.
- To gain institution, Petitioner told the Board: “The [district court] agreed the patent’s claims are all about ‘intent’ and ‘purpose’ and not any specific level of efficacy, construing the preamble language to mean ‘the claimed administration *is for the purpose of* care and management of a patient Type 2 diabetes’ or ‘*is intended to* care for and manage a patient with Type 2 diabetes.”
Pap.7 (Petitioner’s Reply to POPR), 1-2 (emphasis original); POR.10.

Petitioner's References

WO421 Describes a Laundry List Of DPP-4 Inhibitors Combined With GLP-1 Compounds

- WO421 discloses combinations of DPP-4 inhibitors with a laundry list of GLP-1 compounds for treating 59 identified metabolic conditions, explaining “**current monotherapy will fail and treatments with *multiple* drugs will be required.**”

EX1011 (WO421), 1:4-5, 4:20-21, 10:22-11:29;
EX2010 (Rosenstock Decl.), ¶¶66-68, 70; POR.5

- Petitioner failed to address how administering a DPP-4 inhibitor with semaglutide would have affected semaglutide dosing.

POR.26 n.13

- WO421 provides “**specific dosage strengths**” for every GLP-1 analogue **except semaglutide**, and identifies dose increments as small as 5 µg (0.005 milligrams).

EX1011 (WO421), 43:4-19; EX2010 (Rosenstock Decl.), ¶¶74-77; POR.5-6

The GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art.

For example, exenatide is administered twice daily by subcutaneous injection (Byetta, 5-30 µg, particularly 5-20µg, preferably 5-10 µg, **specific dosage strengths are 5 or 10 µg**) before a main meal.

Exenatide LAR is administered once weekly by subcutaneous injection (0.1-3 mg, particularly 0.5 mg to 2.0 mg, **specific dosage strengths are 0.8 mg or 2.0 mg**).

Liraglutide is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, **specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg**).

Taspoglutide is administered once weekly by subcutaneous injection (1-30 mg, **specific dosage strengths are 1 mg, 8 mg, 10 mg, 20 mg or 30 mg**).

Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).

Albiglutide is administered once weekly by subcutaneous injection (4-30 mg, **specific dosage strengths are 4 mg, 15 mg or 30 mg**).

Lixisenatide is administered once daily by subcutaneous injection (10-20 µg, **specific dosage strengths are 10 µg, 15 µg or 20 µg**).

Dulaglutide is administered once weekly by subcutaneous injection (0.25-3 mg, **specific dosage strengths are 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg or 3.0 mg**).

Lovshin Is a Review Article Disclosing “Incretin-Based Therapies” Under Investigation

- Petitioner argues “Lovshin is an article that disclosed treating type 2 diabetes with semaglutide.”

Pet.21
- But Lovshin discloses that “NN9535” was “being *investigated*” (“I”) for once-weekly administration.

EX1012 (Lovshin), Table 1; EX2010 (Rosenstock Decl.), ¶¶79-81; POR.6
- And POSITA would have known that Lovshin’s semaglutide “range” would have been understood by looking to NCT657, which **did not include 1.0mg**.

EX2018 (Bantle Dep. Tr.), 77:4-20;
EX2010 (Rosenstock Decl.), ¶¶269-270; POR.36-37

Table 1 Incretin-based therapies		
Agent	Dose	Status
<i>GLP-1R agonists (subcutaneous injection)</i>		
Exenatide	5–10 µg twice daily	A
Liraglutide	1.2–1.8 mg once daily	F
AVA0010	5–30 µg once or twice daily	I
Exenatide QW	2 mg once weekly	I
Taspoglutide	20–30 mg once weekly	I
Albiglutide	30–50 mg once weekly	I
CJC-1134-PC	1.5–3 mg once or twice weekly	I
NN9535	0.1–1.6 mg once weekly	I
LY2189265	0.25–3 mg once weekly	I
LY2428757	0.5–17.6 mg once weekly	I
<i>DPP-4 inhibitors (oral)</i>		
Sitagliptin	25–100 mg once daily	A
Vildagliptin	50 mg twice daily	A
Alogliptin	12.5–25 mg once daily	F
Saxagliptin	5–10 mg once daily	F
Linagliptin	2.5–5 mg once daily	I
Dutogliptin	200–400 mg once daily	I
Abbreviations: QW, once weekly; A, approved; F, filed for regulatory approval; I, being investigated.		

EX1012 (Lovshin), 2 (Table 1)

Lovshin Is a Review Article Disclosing “Incretin-Based Therapies” Under Investigation (*cont'd*)

- Lovshin warns “few data are available on the structure or efficacy of these [potential once-weekly] molecules.

EX1012 (Lovshin), 5; POR.6

Other long-acting GLP-1R agonists

Additional long-acting GLP-1R agonists in clinical trials include CJC1134 (ConjuChem, Montreal, Canada), a protein that contains an exendin 4 peptide moiety covalently linked to human serum albumin through a chemical linkage, which proved to exert a broad range of GLP-1-receptor-dependent glucose-regulatory actions in preclinical studies.³⁴ Similarly, multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I–II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1), but few data are available on the structure or efficacy of these molecules.

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses (*cont'd*)

- And Petitioner's and PO's experts agree that in understanding **WO421 and Lovshin**, POSITA would have looked to **NCT657** to understand "0.1-1.6," and that NCT657 tested five doses—***none of which were 1.0mg***.

– Per Petitioner's Dr. Bantle:

Q. And do you agree that a -- is it your opinion that a POSITA would have looked to NCT657 to understand the scope of the dose range for semaglutide disclosed by WO421?

A. **Yes. I think a POSA would have looked at that.**

EX2018 (Bantle Dep. Tr.), 78:9-15; POR.21; SurRep.9-10

Q. And had a POSA looked at that, they would have seen that 1 milligram was not part of that disclosed range in NCT657; is that correct?

A. **Yes.**

EX2018 (Bantle Dep. Tr.), 78:16-19, 71:5-13; EX2010 (Rosenstock Decl.), ¶¶210-216; EX1013 (NCT657), 7-8, POR.6, 21; SurRep.9-10

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses (*cont'd*)

Q. And would a POSITA have looked for information about those studies in understanding the disclosed dosages in Lovshin?

A. I think one would have been interested in looking at those studies to help better understand the doses being studied because this is a – you know, it's a one-sentence description. It's not very much information.

Q. Did you look at those studies?

A. I looked at NCT773 and NCT657.

Q. And those two studies that you just references looking at, neither of those studies administered 1 milligram of semaglutide weekly; is that correct?

A. Yes.

EX2018 (Bantle Dep. Tr.), 77:4-20; POR.36; SurRep.9-10

NCT657 Did Not Test 1.0mg

- Petitioner describes NCT657 as “a **Phase II** clinical trial that started in June 2008 and ended in February 2009” that **tested “0.1, 0.2, 0.4, 0.8, and 1.6” milligrams.**

Pet.22; EX1013 (NCT657), 15

- Petitioner thus acknowledges **1.0mg was not tested**, and **Petitioner does not** contend that NCT657 discloses **any results**.

Pet.22; EX1013 (NCT657), 15; EX2010 (Rosenstock Decl.), ¶98; POR.7-8

NCT773 Did Not Test 1.0mg, Let Alone in Patients With T2D

- Petitioner describes **NCT773** as “a **Phase I** clinical trial” with several available versions, including a September 11, 2009 version that included doses of 0.1mg, 0.2mg, 0.4mg, 0.8mg, and 1.6mg, and an October 22, 2011 version which removed the 1.6mg arm and included a 1.2mg arm.
Pet.23-24
- But NCT773 **expressly excluded** subjects with **diabetes** and was a study **including Japanese volunteers**.

EX1014 (NCT773), 8 (“*Exclusion Criteria: ... Presence or history of diabetes*”); EX2010 (Rosenstock Decl.), ¶¶101, 409; POR.8, 77-78; Slide 16

NCT773 Did Not Test 1.0mg, Let Alone in Patients With T2D (*cont'd*)

- NCT773's inclusion criteria states:

Criteria

Inclusion Criteria:

- For Caucasian or Japanese volunteers the following applies:
- Informed consent obtained before any trial-related activities
- Body weight between 54 and 90 kg (both inclusive)
- Body mass index (BMI) between 18.5 and 24.9 kg/m² (both inclusive)
- HbA1c below 6.0 %
- Subjects who are considered to be generally healthy based on assessment of medical history, physical examination and clinical laboratory data at screening, as judged by the Investigator
- Subjects who are sexually active and have partners who are or could be pregnant are willing and required to use a barrier method of contraception (e.g. condom) for the duration of the study and for 90 days following the last dose of study medication
- Japanese passport holder, Japanese-born parents, lived outside Japan for 5 years or less

EX1014 (NCT773), 8; EX2010 (Rosenstock Decl.), ¶103; POR.8-9

NCT773 Did Not Test 1.0mg, Let Alone in Patients With T2D (*cont'd*)

- As Petitioner's Dr. Jusko acknowledged, the 1.2mg arm could have been the result of expected "smaller body sizes."

EX2019 (Jusko Dep. Tr.), 118:9-119:17; POR.8 n.5

Q. Is it possible that the 1.2-milligram dose in NCT773 was lower than the 1.6-milligram dose in NCT657 because plasma concentrations in Japanese people of semaglutide may have been higher than Caucasian people?

A. Well, I don't know fully what Novo Nordisk was thinking. My expectation was that the 1.6, they were finding too many adverse effects and backed off on the dose. But another consideration could be that the pharmaco- -- they did not know the pharmacokinetics ahead of time, so they backed off on dosing as well because of the smaller body sizes.

EX2019 (Jusko Dep. Tr.), 118:9-119:17; POR.8 n.5; see also EX2010 (Rosenstock Decl.), ¶¶167-171, 409, 411; POR.77

- And the portion of EX1014 that is potentially prior art—the September 2009 capture—included the 1.6mg arm, **not** the 1.2mg arm.

EX2010 (Rosenstock Decl.), ¶¶102-105; POR.8-9; Slide 67

'424 Publication Does Not Disclose GLP-1 Dosing Information or Semaglutide

- Petitioner asserts that the '424 Publication discloses “formulations comprising a peptide and propylene glycol” and that it “could be used with **any peptide**, including GLP-1 and derivatives and analogues thereof.”
- But Petitioner **does not contend** the '424 Publication identifies **semaglutide**, or that it discloses **dosing for *any* GLP-1 analogue**.

Pet.25

EX1016 ('424 Publication) 11-13; EX2010 (Rosenstock Decl.), ¶¶111-113; POR.7

WO537 Does Not Disclose Semaglutide Dosages

- Petitioner asserts that WO537 “included claims disclosing semaglutide, injectable formulations of it, and its use to treat type 2 diabetes.”

Pet.25 (citing EX1015 (WO537), 74, 76)

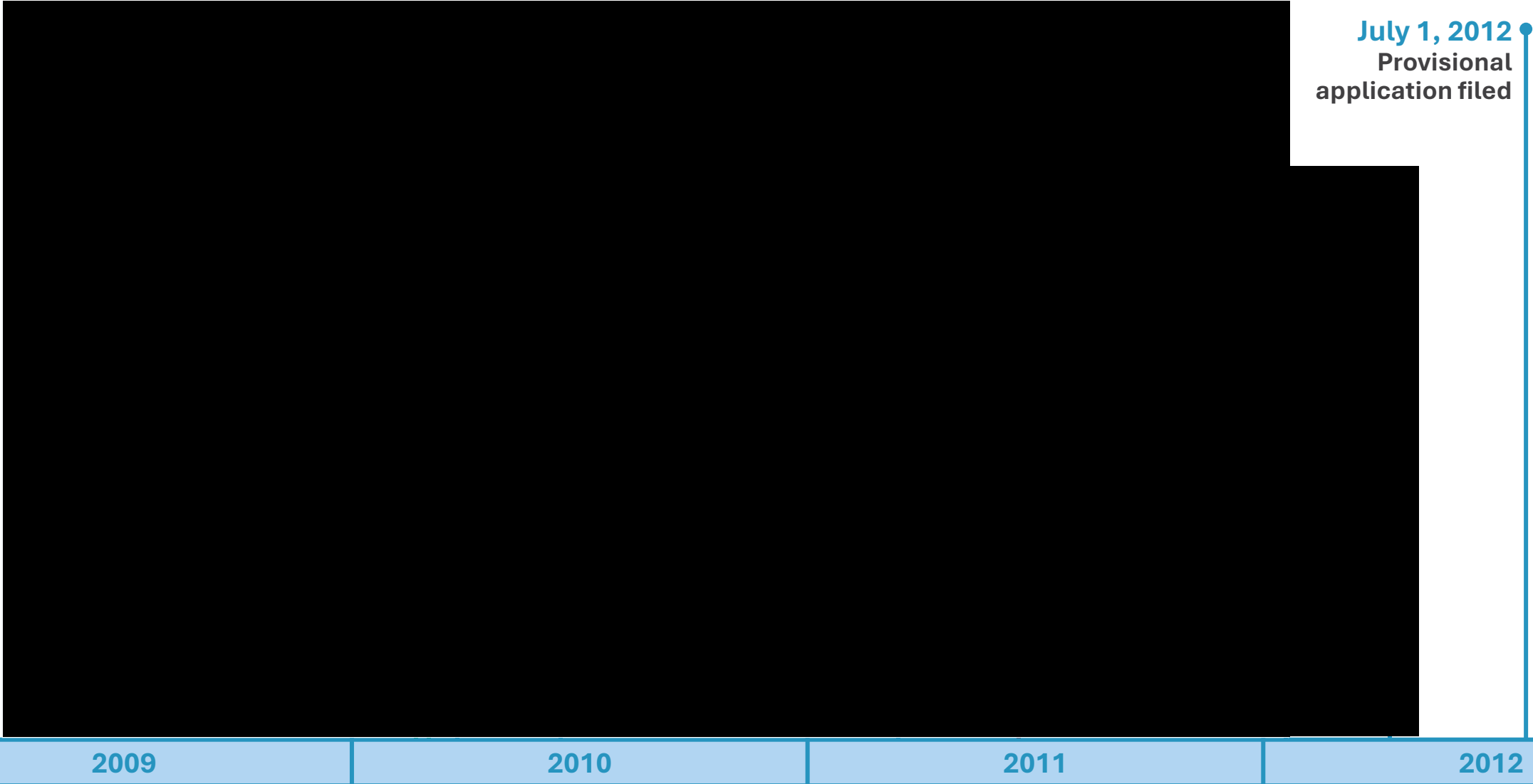
- But WO537 does not disclose a **1.0mg dose for semaglutide**, or that semaglutide would have been **safe, effective, and tolerable** if administered **once weekly** for treatment of **any condition**.

EX2010 (Rosenstock Decl.), ¶¶108-110; POR.9

Grounds 1 and 3: The '462 Patent Antedates WO421

Dr. Christine Jensen Conceived [REDACTED]

[REDACTED] Before WO421's Earliest Effective Prior-Art Date



Dr. Christine Jensen Conceived [REDACTED] [REDACTED] Before WO421's Earliest Effective Prior-Art Date

- WO421's earliest effective prior-art date is **May 5, 2011**.
POR.13; Rep.2, n.3
- Inventor Dr. Christine Jensen performed the mental steps that led to her **conception** of '462 claims 1-3 by at least **March 17, 2010** in New York, and no later than **May 28, 2010** in Denmark (a WTO country), [REDACTED]
[REDACTED].
POR.14-19; SurRep.1-2

- Petitioner *has not disputed* [REDACTED].
See generally Rep.; SurRep.1; see also SurRep.1-9

- Petitioner also *does not dispute* that Dr. Jensen *had the invention in mind* and [REDACTED] before WO421's effective prior-art date.
See generally Rep.; SurRep.1; see also SurRep.1-9

- Petitioner instead disputes **whether Dr. Jensen was the one to *conceive* the invention.**

Rep.2-4, 6-8

- But Petitioner's evidence **does not show that *anyone else* previously conceived the complete invention** (including with its required expectation of **efficacy and tolerability** in “treating” T2D)—and ***only Dr. Jensen* had the [REDACTED]** that led to her conception.

SurRep.2-4, 6; [REDACTED]

EX1312 (Jensen Dep. Tr.), 66:4-67:1, 71:6-8; EX2050 (Jensen Decl.), ¶¶21-26; Slides 34-42

– [REDACTED]

SurRep.4-5; Slides 34-42

- Petitioner has, at most, suggested only that others might have ***contributed*** to Dr. Jensen's **conception**—but **these would, at most, be co-inventors.**

Rep.8; SurRep.2-5 & n.3; Slides 34-42

- And **there is no need to address *inventorship* arguments** to conclude a sworn-behind reference “is not prior art.”

Pfizer, Inc. v. Genentech, Inc., IPR2017-01923, Pap.110, 25 (Apr. 2, 2019); POR.13; e.g., *Ethicon, Inc. v. U.S. Surgical Corp.*, 135 F.3d 1456, 1461 (Fed. Cir. 1998); Slide 63

The Law of Corroboration

- Petitioner's only other dispute is whether the voluminous evidence **corroborating Dr. Jensen's conception** is sufficient.
- But Petitioner **ignores what the governing *rule of reason* actually requires for corroboration.**

Rep.5-7; SurRep.1, 7

SurRep.6-7

The Law of Corroboration (*cont'd*)

[C]orrobor[ation] is evaluated under a **“rule of reason” analysis [requiring] “[a]n evaluation of all pertinent evidence... so that a sound determination of the credibility of the alleged inventor’s story may be reached.”**

Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461 (Fed. Cir. 1998); SurRep.6

Circumstantial evidence about the inventive process, **alone, may... corroborate.**

Sandt Tech., Ltd. v. Resco Metal & Plastics Corp., 264 F.3d 1344, 1351 (Fed. Cir. 2001); SurRep.7

- **“Element-wise attack[s] on corroboration” should be “rejected.”**

TransWeb, LLC v. 3M Innovative Props. Co., 812 F.3d 1295, 1302 (Fed. Cir. 2016); SurRep.6

The Law of Conception

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.”

E.g., REG Synthetic Fuels, LLC v. Neste Oil Oyj, 841 F.3d 954, 962 (Fed. Cir. 2016) (emphases modified); POR.11; SurRep.1

An idea is sufficiently definite for conception “when the inventor has a **specific, settled idea**, a particular solution to the problem at hand, **not just a general goal or research plan** he hopes to pursue.”

E.g., Creative Compounds, LLC v. Starmark Lab’ys, 651 F.3d 1303, 1312 (Fed. Cir. 2011); SurRep.4

A “**preliminary**” statement about a “**possibility**”... alongside a **recommendation for continued work** and a [future] “**report back**”... falls short...”

Dawson v. Dawson, 710 F.3d 1347, 1353 (Fed Cir. 2013); SurRep.4

- “[S]imply a **wish to know**” is **not conception**.

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991); SurRep.4

The Claimed “Method for Treating” T2D Requires Expectations of Both Efficacy and Tolerability

- Petitioner argues Dr. Jensen’s analysis of [REDACTED] is irrelevant to conception. Rep.4-5
- But Dr. Jensen’s described mental path to the invention is pertinent to how and when she conceived. SurRep.3
- And **the parties’ experts agree that “treating” requires an expectation of both tolerability and efficacy.**

Slides 6, 28-29; EX2010, ¶305; Inst.23; POR.10-11, 45; SurRep.2.;

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

The Claimed “Method for Treating” T2D Requires Expectations of Both Efficacy and Tolerability (*cont'd*)

- But Petitioner **ignores** these agreed requirements of **tolerability** and **efficacy**, even though its own experts confirmed they are required.
 - Per Petitioner’s Dr. Jusko:

[I]f the patient **won’t accept treatment**, then **it’s not a treatment**.

EX2553 (Jusko Dep. Tr.), 14:7-15:4; SurRep.1-2

[T]reating diabetes **requires clinically meaningful change**.

EX2553 (Jusko Dep. Tr.), 41:3-15 (“statistically insignificant [HbA_{1c}] decrease” “[p]robably not” claimed “treating”); SurRep.1-2

[T]he goal is to have **as much efficacy without toxicity**.

EX2019 (Jusko Dep. Tr.), 128:6-16; SurRep.2

The Claimed “Method for Treating” T2D Requires Expectations of Both Efficacy and Tolerability (*cont'd*)

– And Per Petitioner’s Dr. Spiegel:

Q. So in your opinion, what is -- what does it mean to treat type 2 diabetes with semaglutide? What is required for it to be a treatment of type 2 diabetes??

A. **What’s required is that there be an acceptable safety and tolerability profile -- and this is not reflected in the patent, this is me, as a physician -- and that it be effective at a given dose and a given frequency of administration in lowering the hemoglobin A1c.**

EX2556 (Spiegel Dep. Tr.), 88:8-18; SurRep.1-2, 18

– PO’s Dr. Rosenstock confirmed the same.

See also EX2010 (Rosenstock Decl.), ¶¶305, 240-258; Pet.14-15 (“to **alleviate or reduce** [T2D] symptoms and complications...”); POR.45; SurRep.1-2

Dr. Jensen Was the Person [REDACTED] [REDACTED] for Treating T2D With Semaglutide

- Dr. Jensen was **the medical director of PO's semaglutide project** beginning in September 2007, just as PO was [REDACTED] from NN9535-1820 (the “1820 Trial”), PO's first in-human dose study of semaglutide in healthy male volunteers.

EX2050 (Jensen Decl.), ¶¶10, 22; EX2051 (Flint Decl.), ¶¶4-5; POR.14-16

- In that role, Dr. Jensen **shepherded the clinical development plan** for semaglutide for T2D, and ***she was the one responsible for determining the treatment dose for T2D.***

EX2050 (Jensen Decl.), ¶¶10-13; EX2051 (Flint Decl.), ¶¶4-5; EX1312 (Jensen Dep. Tr.), 104:1-13 (“[REDACTED]”); POR.14-16; SurRep.9

- Based on the results of the 1820 Trial, Dr. Jensen designed a Phase II dose-range-finding study, NN9535-1821 (NCT657) (the “1821 Trial”), to evaluate several once-weekly subcutaneous doses—but not 1.0mg—in patients with T2D.

EX2050 (Jensen Decl.), ¶11; POR.14-15; SurRep.3

- By [REDACTED], Dr. Jensen received the completed confidential 1821 Trial data, which showed her that certain of the tested doses were effective at reducing HbA_{1c}.

EX2050 (Jensen Decl.), ¶¶12-13; [REDACTED]
[REDACTED] 14, 67; EX1001 ('462 Patent), Figs.1-5;
POR.15; SurRep.3

- But Dr. Jensen also determined from the data that higher tested doses of semaglutide led to decreased tolerability and increased rates of subject withdrawals.

EX2050 (Jensen Decl.), ¶¶12-13; [REDACTED]
[REDACTED], 14, 67; EX1001 ('462 Patent), Figs.1-5; POR.15; SurRep.3

- Dr. Jensen continued to analyze issues of [REDACTED], including whether other doses would be appropriate to test in Phase III trials.

EX2050 (Jensen Decl.), ¶¶16-17; POR.15; SurRep.3

- Dr. Jensen focused on how to improve [REDACTED]

EX2050 (Jensen Decl.), ¶¶16-17;

[REDACTED]; POR.15; SurRep.3

Until Dr. Jensen's Conception, Which Dose to Use [REDACTED]

- With the results of the 1821 Trial in hand, Dr. Jensen (and others at Novo) continued to [REDACTED].

EX2050 (Jensen Decl.), ¶¶14-16; POR.15; SurRep.3-5

- Petitioner argues that “others suggested th[e] idea” of “a once-weekly 1.0mg semaglutide dose to treat T2D.”

Rep.4, 8

- But Petitioner presented no evidence indicating Dr. Jensen “derived” or “reproduced” an **already-conceived invention**.

Rep.2-4, 6; SurRep.2-4

- Petitioner never even attempts to show anyone else previously conceived a **permanent** and **definite** idea of the **complete invention** with an expectation of [REDACTED], as the claims require.

Rep.2-4, 6; SurRep.4-5; Slides 22-23, 35-42

- Instead, **which dose—and whether 1.0mg should be used—to treat T2D** [REDACTED]

POR.14-16; SurRep.4-5

Until Dr. Jensen's Conception, Which Dose to Use

(cont'd)

- For example, in the [REDACTED] email relied on by Petitioner (Rep.4), [REDACTED]

[REDACTED] POR.15; SurRep.4-5

Until Dr. Jensen's Conception, Which Dose to Use [REDACTED]

ont'd)

- Petitioner argues that, in this email, [REDACTED]

Rep.2, 4

- But far from a **definite, permanent** idea of the complete claimed invention (which requires expectations of **efficacy and tolerability**), [REDACTED]

[REDACTED]; Rep.2, 4; SurRep.3-5

- A mere suggestion is *not* conception.

SurRep.3-5

- “[A] general goal . . . [they] hope[d] to pursue” is not conception.

Creative Compounds, LLC v. Starmark Lab'ys, 651 F.3d 1303, 1312 (Fed. Cir. 2011); SurRep.4-5

- “A ‘preliminary’ statement about a ‘possibility’... alongside a recommendation for continued work and a [future] ‘report back’... falls short” of conception.

Dawson v. Dawson, 710 F.3d 1347, 1353 (Fed Cir. 2013) ; SurRep.4-5

- “[S]imply a wish to know” is not conception.

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1206 (Fed. Cir. 1991); SurRep.4

Until Dr. Jensen's Conception, Which Dose to Use

(cont'd)

- And, contrary to Petitioner's assertions (Rep.4), Dr. Jensen did **not** admit that

:

Rep.4 (citing EX1312 (Jensen Dep. Tr.), 21:14-22:8, 26:8-14, X1312 (Jensen Dep. Tr.), 26:15-22; SurRep.3-5, n.4

Q. All right. In fact, you were not the first person at Novo Nordisk, correct?

A. I think .

Q. And among those suggestions was a suggestion to potentially

A. I think it was suggested at .

EX1312 (Jensen Dep. Tr.), 21:14-22:8; SurRep.4-5

Q. So in this e-mail Dr. correct?

A. Yes, he's -- well, I don't know if he's doing that, but he's asking me to look into the difference

EX1312 (Jensen Dep. Tr.), 26:15-22; SurRep.4

Until Dr. Jensen’s Conception, Which Dose to Use [REDACTED]

[REDACTED] (cont'd)

- In [REDACTED]
[REDACTED].
EX1312 (Jensen Dep. Tr.), 30:1-31:19, 37:3-12; [REDACTED] SurRep.4-5

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

EX1312 (Jensen Dep. Tr.), 31:12-19, 37:3-12; SurRep.4-5

Until Dr. Jensen's Conception, Which Dose to Use

(cont'd)

- In [REDACTED], Dr. Jensen and her team [REDACTED] that

[REDACTED]; SurRep.4; see *also* POR.15-16

Until Dr. Jensen's Conception, Which Dose to Use

(cont'd)

- Dr. Flint confirmed that which

EX2051 (Flint Decl.), ¶¶4-5; POR.15

Until Dr. Jensen's Conception, Which Dose to Use

(cont'd)

- And in comments Dr. Jensen noted in her

EX1312 (Jensen Dep. Tr.), 26:15-22 ([REDACTED]); EX2050 (Jensen Decl.), ¶¶14-16, 18;
EX2051 (Flint Decl.), ¶¶4-5; POR.15; SurRep.4-5

[REDACTED]; POR.15

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK)

- On [REDACTED], Dr. Jensen [REDACTED]

2; EX2050, ¶¶18-19; POR.15-16; SurRep.2, 7

POR.15-16

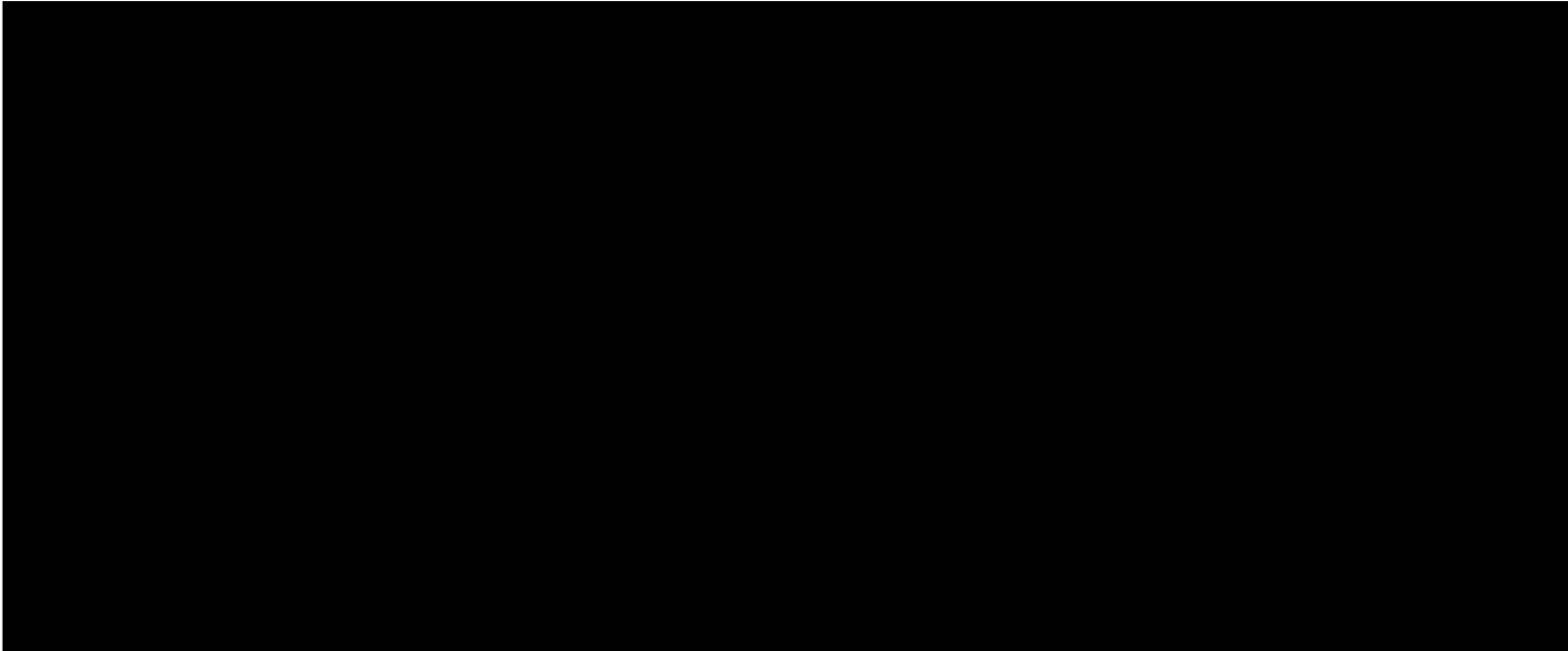
Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (*cont'd*)

- On [REDACTED] Dr. Jensen requested were sent to her.

[REDACTED]; POR.15-16; SurRep.4-5, 7

[REDACTED] POR.15-16; SurRep.4-5, 7

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) *(cont'd)*



Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (*cont'd*)

- Dr. Jensen also separately determined [REDACTED]

EX2050 (Jensen Decl.), ¶¶19, 21; [REDACTED]

POR.15-16

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (cont'd)

- Based on [REDACTED]

EX2050 (Jensen Decl.), ¶¶18-21;

[REDACTED], 5, 7; POR.15-16; SurRep.2-3

- Dr. Jensen was [REDACTED] to decide on the 1.0mg regimen.

EX1312 (Jensen Dep. Tr.), 71:6-8; EX2050 (Jensen Decl.), ¶¶21-26; POR.16; SurRep.2-4

Q. Okay. Did other folks on the project team analyze the modeling data?

A. No.

EX1312 (Jensen Dep. Tr.), 71:6-8; SurRep.2

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (*cont'd*)

- Petitioner’s criticism that this last step didn’t require much time ignores both Dr. Jensen’s scientific analysis and the massive effort (including the 1821 trial) making that step possible.

Rep.3; SurRep.3; Slides 30-46

- Petitioner’s criticism also ignores the law.

Rep.3; SurRep.3

“Patentability shall *not* be negated by the manner in which the invention was made.”

35 U.S.C. § 103; SurRep.3

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (*cont'd*)

- On **March 17, 2010**, Dr. Jensen met confidentially [REDACTED]
[REDACTED] in New York [REDACTED]

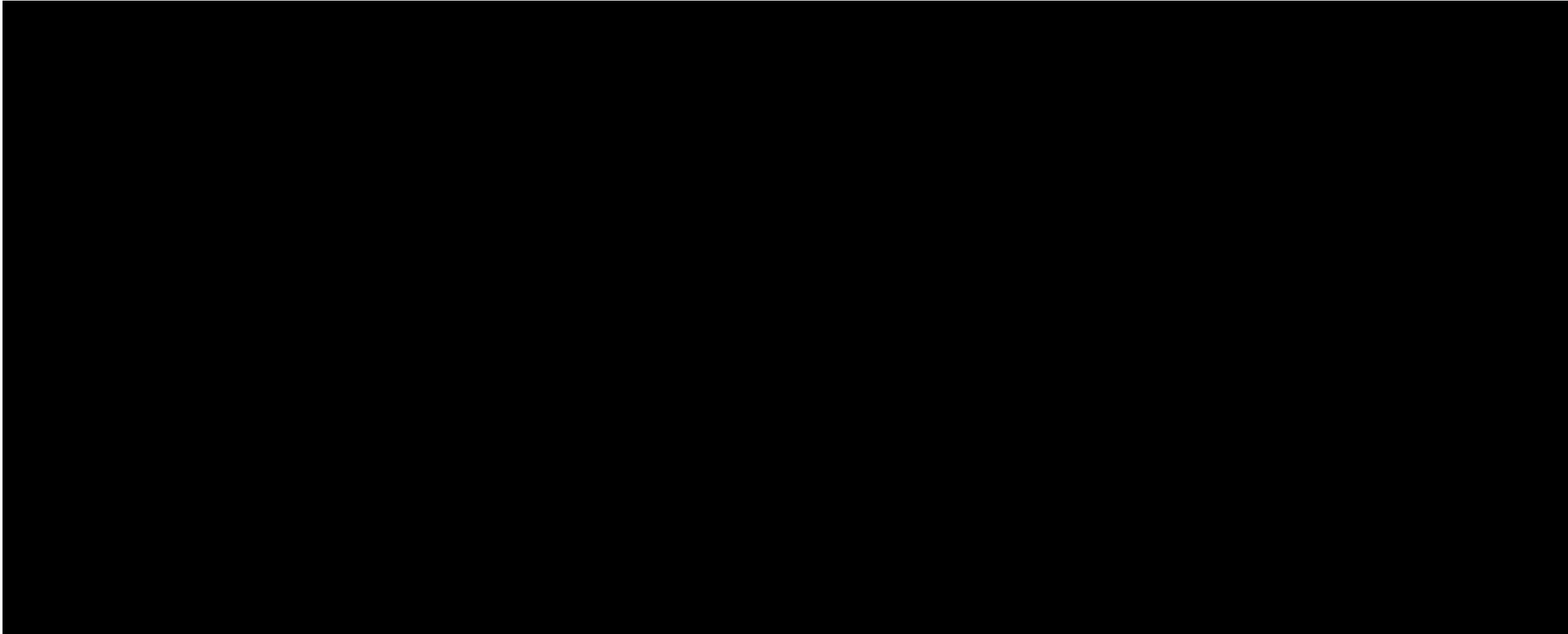
EX2050 (Jensen Decl.), ¶22;

; POR.16

Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) *(cont'd)*



Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) *(cont'd)*



Dr. Jensen Conceived of the Inventions of Claims 1-3 at Least by March 17, 2010 (NY) and No Later Than May 28, 2010 (DK) (cont'd)

- On **May 28, 2010**, Dr. Jensen and her team also presented her invention to [REDACTED] in Denmark.

EX2050 (Jensen Decl.), ¶¶23-26; [REDACTED]

; POR.16

- Dr. Jensen's dosing regimen is what was "thereafter [] applied" [REDACTED]

REG Synthetic Fuels, LLC v. Neste Oil Oyj, 841 F.3d 954, 962 (Fed. Cir. 2016); Slides 20-21; SurRep.6

- Petitioner criticizes this work as being about "study design."

Rep.4-5, 8

- But this mistakenly conflates **conception** with **reduction-to-practice**, which 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); SurRep.6 n.5

- Petitioner's attempts, e.g., to dismiss as irrelevant her described mental path are baseless: these are pertinent to how and when she conceived.

Slides 25-26; *Sandt Tech., Ltd. v. Resco Metal & Plastics Corp.*, 264 F.3d 1344, 1351 (Fed. Cir. 2001) ("Circumstantial evidence about the inventive process, alone, may... corroborate"); Rep.3-5; SurRep.3, 7

Petitioner's Criticisms Ignore the Law on Corroboration

- 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, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461 (Fed. Cir. 1998) (cleaned up); SurRep.6

- **“Element-wise attack[s] on corroboration” should be “rejected.”**

TransWeb, LLC v. 3M Innovative Props. Co., 812 F.3d 1295, 1302 (Fed. Cir. 2016); SurRep.6

- “At bottom, the goal of the analysis is to determine ‘whether the inventor's story is credible.’”

NFC Tech., LLC v. Matal, 871 F.3d 1367, 1372 (Fed. Cir. 2017); SurRep.6-7

- “Corroborating evidence may take many forms” and doesn’t require “corroborat[ing] every [contested] factual issue.”

Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461, 1464 (Fed. Cir. 1998); SurRep.6-7

Petitioner's Criticisms Ignore the Law on Corroboration (*cont'd*)

- Corroboration does not require “an... over-the-shoulder observer.”
Cooper v. Goldfarb, 154 F.3d 1321, 1330 (Fed. Cir. 1998); SurRep.7
- Corroboration does not require a single explicitly-corroborating document—“an inventor's conception can be corroborated **even though no one piece of evidence in and of itself establishes that fact.**”
NFC Tech., LLC v. Matal, 871 F.3d 1367, 1372 (Fed. Cir. 2017) (cleaned up); SurRep.7
- **“Circumstantial evidence about the inventive process, alone, may also corroborate.”**
Sandt Tech., Ltd. v. Resco Metal & Plastics Corp., 264 F.3d 1344, 1351 (Fed. Cir. 2001); SurRep.7

Dr. Jensen's Conception Is Amply Corroborated With Evidence Specific to Her

- **Multiple contemporaneous documents** corroborate Dr. Jensen's invention story, including:

- [REDACTED]
- [REDACTED]
- [REDACTED]

EX2050 (Jensen Decl.), ¶¶10-26; POR.14-16; SurRep.6; Slides 43-52

- Dr. Flint's testimony also confirms Dr. Jensen's invention story, [REDACTED]

[REDACTED]

EX2051 (Flint Decl.), ¶¶4-5; SurRep.6

Dr. Jensen’s Conception Is Amply Corroborated With Evidence Specific to Her *(cont'd)*



Dr. Jensen's Conception Is Amply Corroborated With Evidence Specific to Her (*cont'd*)

- Petitioner complains some of PO's corroborating evidence pre-dates conception.

Rep.5-6 (criticizing [REDACTED])

- But Petitioner never disputes the **content** of these documents, which **directly evidence Dr. Jensen's inventive process**, and **strongly corroborate her resulting conception**.

E.g., Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461 (Fed. Cir. 1998); SurRep.7

- Petitioner improperly criticizes the evidence in piecemeal fashion, ignoring that these documents **confirm Dr. Jensen's investigation into a viable dosing regimen, which she testified led ultimately to her conception**.

See, e.g., EX2050 (Jensen Decl.), ¶¶10-17; SurRep.7

- [REDACTED]

EX2050 (Jensen Decl.), ¶¶18-21; SurRep.7

Dr. Jensen's Conception Is Amply Corroborated With Evidence Specific to Her (*cont'd*)

- Petitioner attacks PO's corroborating documents for "not t[ying] the idea of 1.0mg to Jensen."

Rep.6 (criticizing [REDACTED])

- But Petitioner ignores that:

- These documents show the claimed dosing regimen **had been conceived by the time of the documents.**
- **Dr. Jensen's name is on each document** as an **author, presenter, and/or participant.**

SurRep.8

POR.14-16; SurRep.8

- Petitioner incorrectly [REDACTED].

EX2050 (Jensen Decl.), ¶¶17, 24, 26; Rep.6; POR.16; SurRep.8, n.6

- Petitioner falsely implies that Dr. Jensen [REDACTED]

Rep.6; SurRep.8

- But Dr. Jensen repeatedly corrected counsel's [REDACTED]

EX1312 (Jensen Dep. Tr.), 101:4-20; SurRep.8

- Petitioner **never attempts to show that anyone other than Dr. Jensen named on these documents was actually the one to have conceived** the invention.

Slides 22-23, 34-42

Dr. Jensen's Conception Is Amply Corroborated With Evidence Specific to Her (*cont'd*)

- Petitioner's case law citations are inapt
 - *NFC* didn't rely solely on an inventor-authored data-sheet, but instead on multiple documents—including a "PCB layout" *not naming the inventor*.
Rep.6; *NFC Tech., LLC v. Matal*, 871 F.3d 1367, 1372-73 (Fed. Cir. 2017); SurRep.8
 - Here, PO's evidence all names Dr. Jensen.
POR.14-16; SurRep.8
 - *Weaver* involved undated photos and a manual authored by individuals *other than the putative inventor*, without explaining how the evidence supported the putative inventor.
Rep.6; *Weaver v. Houchin*, 467 Fed. App'x 878, 881 (Fed. Cir. 2012) (non-precedential); SurRep.8-9
 - Here, PO has explained how the evidence corroborates Dr. Jensen's conception.
POR.14-16; SurRep.2, 6-9

Petitioner’s Efforts to Suggest That Others Conceived of the Invention Fail

- Petitioner has not shown any evidence that others conceived of the invention.

Slides 22-23, 34-42; SurRep.3-4

 - Overcoming the presumption of correct inventorship requires clear and convincing evidence in AIA proceedings.

Incyte Corp. v. Concert Pharms., Inc., PGR2021-00006, Pap.70, 11-16 (Oct. 11, 2022); *Hess v. Advanced Cardiovascular Sys., Inc.*, 106 F.3d 976, 980 (Fed. Cir. 1997); SurRep.4-5 & n.3
 - No evidence indicates Dr. Jensen “derived” or “reproduced” an already-conceived invention.

Rep.4 (citing *Solvay S.A. v. Honeywell Int’l*, 622 F.3d 1367, 1376-1379 (Fed. Cir. 2010)); SurRep.3-5
 - [REDACTED]
 - No one except Dr. Jensen had, [REDACTED] leading to Jensen’s conception.

Compare, e.g., [REDACTED] see also EX1312 (Jensen Dep. Tr.), 71:6-8; Slides 43-47
 - [REDACTED]

Petitioner's Efforts to Suggest That Others Conceived of the Invention Fail (*cont'd*)

- These are mere suggestions that [REDACTED]
[REDACTED]
Rep.4 ([REDACTED]), 2); EX1312 (Jensen Dep. Tr.), 22:1-18; SurRep.3-5
- Nor, as noted above, did Dr. Jensen [REDACTED]
[REDACTED].
Rep.4; SurRep.4, n.4; Slide 38
- And again, which doses and whether 1.0mg should be used to treat T2D [REDACTED]
[REDACTED]
Rep.2-3; [REDACTED]
EX1312 (Jensen Dep. Tr.), 21:14-22:8, 30:1-31:19, 37:3-12; SurRep.4-5; Slides 34-42

[W]here the idea is in constant flux, it is not definite and permanent.

Burroughs Wellcome Co. v. Barr Lab'ys, 40 F.3d 1223, 1229 (Fed. Cir. 1994)

- Petitioner (Rep.7) also ignores that Dr. Flint confirmed that Dr. Jensen, [REDACTED]
[REDACTED] (EX2051 (Flint Decl.), ¶15), further corroborating
Dr. Jensen's testimony it was "[Dr. Jensen's] role" to "[REDACTED]".
EX1312 (Jensen Dep. Tr.), 104:10-13; SurRep.9; Slide 55

Petitioner's Efforts to Suggest That Others Conceived of the Invention Fail (*cont'd*)

- Petitioner complains that PO's exhibits don't "identify [Dr. Jensen] as the source of [the 1.0mg] dose."

Rep.6

- But as Dr. Flint testified, these aren't the type of documents to do so.

E.g., EX1311 (Flint Dep. Tr.), 87:5-14, 69:2-70:10; SurRep.9

- "Corroborating evidence may take many forms" and doesn't require "corroborat[ing] every [contested] factual issue" or "an... over-the shoulder observer."

Ethicon, Inc. v. U.S. Surgical Corp., 135 F.3d 1456, 1461, 1464 (Fed. Cir. 1998); *Cooper v. Goldfarb*, 154 F.3d 1321, 1330 (Fed. Cir. 1998); SurRep.6-7

- Dr. Flint never claimed to cite documents "demonstrat[ing] the 1.0mg dose came from Jensen."

Rep.7; SurRep.9

- Instead, Dr. Flint's corroborating testimony was based on her own recollection of work on the semaglutide team.

E.g., EX1311 (Flint Dep. Tr.), 77:3-78:1; SurRep.9

Petitioner's Efforts to Suggest That Others Conceived of the Invention Fail (*cont'd*)

- Even if the Board were to credit Petitioner's unsupported arguments about someone else **contributing** to Dr. Jensen's conception, this **would not negate** Dr. Jensen's **conception**.

Rep.8; SurRep.5

 - At most, 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”); SurRep.5
 - Nor can Petitioner carry its burden on WO421.

E.g., Incyte Corp. v. Concert Pharms., Inc., PGR2021-00006, Pap.70, 11-16 (Oct. 11, 2022) (confirming “presumption of correct inventorship” applies in AIA proceedings); SurRep.5; Slides 69-110

It Is Undisputed That Dr. Jensen

•

[REDACTED]

EX2050 (Jensen Decl.), ¶¶8, 29, 30; EX2051 (Flint Decl.), ¶¶8-10; [REDACTED]; POR.17-18

•

[REDACTED]

See, e.g., EX2050 (Jensen Decl.), ¶¶8, 30-31; EX2051 (Flint Decl.), ¶¶8-10; [REDACTED], 3, 27-28, 37-38; POR.18

•

[REDACTED]

EX2050 (Jensen Decl.), ¶¶8, 32-33; EX2051 (Flint Decl.), ¶¶11-13; [REDACTED] 1, 3; [REDACTED] POR.18

It Is Undisputed That Dr. Jensen

(cont'd)

- [REDACTED]

POR.19

- [REDACTED]

EX2050 (Jensen Decl.), ¶¶8, 33; EX2051 (Flint Decl.), ¶13; POR.19

Ground 5: The '462 Patent Antedates NCT773

Ground 5: NCT773 Is Not Prior Art for the Same Reason That WO421

- Petitioner asserts NCT773 is prior art to the '462 Patent and that the earliest version of is dated Sept. 11, 2009.
Rep.2 n.2
- But NCT773's disclosure of a **1.2mg maximum dose** (on which Petitioner relies) is dated **Oct. 22, 2011**, which is **antedated by claims 1-3 of the '462 Patent**.
EX1014 (NCT773), 6-9; POR.73-74; Slides 14, 21
- Petitioner's reliance on the Sept. 11, 2009 screen capture reflects a **1.6mg maximum dose** just like NCT657 (considered during prosecution).
EX1014 (NCT773), 11; POR.74; Slide 14
- Petitioner's reliance on the Dec. 27, 2011 screen capture, which purports to disclose the study being completed in 2009, was also information **not known to POSITA** as of the priority date at least because it, too, was not prior art to claims 1-3.
EX1014 (NCT773), 4-5; EX2010 (Rosenstock Decl.), ¶399; POR.74

Petitioner's Grounds 1-2 Fail

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses

- Petitioner asserts the “genus” of “0.1-1.6mg” would be understood as “a disclosure of a discrete and limited class of doses a POSA can at once envisage.”
Pet.30
- But neither WO421 nor Lovshin tells POSITA about **particular doses** or **any dosing increments**.
EX1011 (WO421), 43:1-19; EX1012 (Lovshin), 2 (Table 1); EX2010 (Rosenstock Decl.), ¶¶74-77, 79-81; POR.5-6
- POSITA would have looked to other references “for any light they shed on what [the allegedly anticipatory reference] would have meant to those skilled in the art.”

Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724, 726-27 (Fed. Cir. 1984); *Galderma Lab'ys, L.P. v. Teva Pharms. USA, Inc.*, 799 F. App'x 838, 843-44 (Fed. Cir. 2020); EX2010 (Rosenstock Decl.), ¶213; EX2018 (Bantle Dep. Tr.), 66:4-15; POR.22

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses (*cont'd*)

- And Petitioner's and PO's experts agree that in understanding **WO421 and Lovshin**, POSITA would have looked to **NCT657** to understand "0.1-1.6," and that NCT657 tested five doses from 0.1 to 1.6mg—***none of which were 1.0mg***.

– Per Petitioner's Dr. Bantle:

Q. And do you agree that a -- is it your opinion that a POSITA would have looked to NCT657 to understand the scope of the dose range for semaglutide disclosed by WO421?

A. **Yes. I think a POSA would have looked at that.**

EX2018 (Bantle Dep. Tr.), 78:9-15; POR.21

Q. And had a POSA looked at that, they would have seen that 1 milligram was not part of that disclosed range in NCT657; is that correct?

A. **Yes.**

EX2018 (Bantle Dep. Tr.), 78:16-19, 71:5-13; EX2010 (Rosenstock Decl.), ¶¶210-216; EX1013 (NCT657), 7-8; POR.6, 21

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses (*cont'd*)

Q. And would a POSITA have looked for information about those studies in understanding the disclosed dosages in Lovshin?

A. **I think one would have been interested in looking at those studies to help better understand the doses being studied because this is a -- you know, it's a one-sentence description. It's not very much information.**

Q. Did you look at those studies?

A. **I looked at NCT773 and NCT657.**

Q. And those two studies that you just referenced looking at, neither of those studies administered 1 milligram of semaglutide weekly; is that correct?

A. **Yes.**

EX2018 (Bantle Dep. Tr.), 77:4-20; POR.36

WO421 and Lovshin Would Be Understood as Disclosing NCT657's 5 Tested Doses (*cont'd*)

- PO's Dr. Rosenstock confirms that:

POSITA would have looked to Novo Nordisk's then-ongoing NCT657 clinical trial... to understand WO421's [and Lovshin's] "range," and based on that, would have understood WO421's [and Lovshin's] "range" to include only the following doses that increase by *doubling* in amount: 0.1 mg, 0.2 mg, 0.4 mg, 0.8mg, and 1.6 mg.

EX2010 (Rosenstock Decl.), ¶¶210-217, 269-271; POR.21, 36

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments

- Petitioner asserts that WO421 and Lovshin disclose “at most” 16 doses in 0.1mg increments based on “Prior art clinical trials for **semaglutide** [which] adjusted doses in increments no less than 0.1 mg/dose.”
Pet.31
- But Petitioner's hindsight-driven rewriting of the “genus” is arbitrary and improper, and using increments **other than** 0.1mg/dose (as was **actually done** with the known semaglutide trials) would **not** lead to the claimed 1.0mg regimen.
POR.20-30; SurRep.11
- Petitioner ignores the **dose doubling** scheme of the NCT657 clinical trial actually testing semaglutide, with **non-0.1-mg intervals**, including intervals of 0.2mg, 0.4mg, and 0.8mg.

EX2010 (Rosenstock Decl.), ¶235; EX2019 (Jusko Dep. Tr.), 82:15-83:16
(“Your hypothetical would be 0.1, 0.2, 0.4, 0.8, 1.6 because those are doubling. **Oh, my gosh. That matches their regimen.**”); POR.29-30

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

- Petitioner also argues POSITA would have looked to **liraglutide's** dosing increments of 0.6mg.

Pet.31-32 (Citing EX1003 (Bantle Decl.), ¶¶256-260, EX1005 (Jusko Decl.), ¶¶189-192); POR.23

- But Petitioner's **0.6mg dosing increment** *would exclude* the claimed **1.0mg** regimen.

EX2010 (Rosenstock Decl.), ¶235; POR.29-30

- And Petitioner never explains why POSITA would have ignored these *0.6mg* dosing increments to get, instead, to Petitioner's argued *0.1mg* dosing increments.

EX2010 (Rosenstock Decl.), ¶235; POR.29-30

- Petitioner's argument that its arbitrarily-declared dosing increments would lead to a **total of 16 doses (contrary to the actual dosing for both semaglutide and liraglutide) also ignores the many known dosing increments** for GLP-1 receptor agonists ***smaller than 0.1mg***.

EX1011 (WO421), 43:1-19; EX2068 (Victoza Prescribing Information), 12; EX2010 (Rosenstock Decl.), ¶¶224-233; POR.23-28

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

- The parties and experts **agree** POSITA would look to dosing increments for other GLP-1 agonists:

Q. Okay. And in determining whether a reference -- that the references in your report anticipate, do you agree that a person of ordinary skill in the art would have looked to information about other GLP-1 analogs for information about semaglutide?

A. Yes. **I think one would look at other analogs** to get some understanding of the class effects and how a new drug might work.

EX2018 (Bantle Dep. Tr.), 49:17-50:4; POR.21, 23; SurRep.12 n.9

- Petitioner and its experts relied on **liraglutide** information: “The liraglutide prior art disclosed dose increments in 0.6 mg increments. A POSA’s knowledge that liraglutide was administered in large dosing increments of 0.6, 1.2, and 1.8 mg reinforced that POSAs would not expect dose adjustments smaller than 0.1 mg to be meaningful for semaglutide.”

Pet.31-32; EX1003 (Bantle Decl.), ¶¶256-260; EX1005 (Jusko Decl.), ¶¶189-192; POR.23

- But **liraglutide** was tested in **dose increments of five ten thousandths of a milligram.**

EX2075 (Madsbad), 1 (“five fixed-dosage groups of liraglutide (0.045, 0.225, 0.45, 0.60, or 0.75 mg)”; EX2068 (Victoza Prescribing Information), 12 (“7.5mcg/kg”); EX2010 (Rosenstock Decl.), ¶231; POR.25

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments *(cont'd)*

- And other GLP-1 agonists were also administered in dosed adjustments far smaller than 0.1mg:

Q. Dr. Bantle, before we lost our connection, I had asked the question, in forming your opinions, did you take into account the fact that WO421 discloses that GLP-1 analogs, such as dulaglutide, are not administered in doses that are exactly tenths of a milligram?

A. **Yes. We, in looking at WO421, could see that some GLP-1 analogs were administered in microgram amounts, exenatide being an example I'm familiar with, and others, like liraglutide and semaglutide, were administered in milligram amounts.**

Q. *So some GLP-1 analogs are administered in microgram amounts?*

A. **Yes.**

EX2018 (Bantle Dep. Tr.), 54:8-22; SurRep.12 n.9

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

Q. In order to inform the dosing increments of semaglutide, would a person of skill in the art have looked to the dosing increments used in other GLP-1 analogs?

A. **They certainly would in part.** What is done with **other drugs in the class can be very informative.**

EX2019 (Jusko Dep. Tr.), 83:17-84:2; POR.23

Q. Right. So I'm asking you, would a person of skill in the art have looked to dulaglutide to inform the dosing regimen of semaglutide?

A. **Certainly.** It doesn't mean we pick the same one.

EX2019 (Jusko Dep. Tr.), 86:15-20; POR.23

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

- As Dr. Rosenstock confirmed:

[A]s Dr. Bantle and Dr. Jusko agree, POSITA reading WO421 would have looked to the dosing increments of other GLP-1 receptor agonists for information about semaglutide and seen that increments other than 0.1 mg (the increment that Dr. Bantle and Dr. Jusko opine would have been used) were used.

EX2010 (Rosenstock Decl.), ¶222; POR.23

- Dosing in 0.05mg increments was common for GLP-1 analogues, and dulaglutide included doses of 0.25mg and 0.75mg.

EX1011 (WO421), 43:18-19; EX2010 (Rosenstock Decl.), ¶¶224-226; Pet.31; POR.24

- Petitioner's expert Dr. Jusko confirmed 0.25mg is a "common dosage unit for a lot of drugs."

EX2019 (Jusko Dep. Tr.), 53:22-54:9; POR.24 n.10

- **Liraglutide** was tested in dose increments of *five ten thousandths of a milligram*.

EX2075 (Madsbad), 1 ("five fixed-dosage groups of liraglutide (0.045, 0.225, 0.45, 0.60, or 0.75 mg)"; EX2068 (Victoza Prescribing Information), 12 ("7.5mcg/kg"); EX2010 (Rosenstock Decl.), ¶231; POR.25

- And the first-in-human **semaglutide** trials dosed based on weight, resulting in doses that were *not* tenths-of-a-milligram: Instead, the Phase I study disclosed doses of 0.625 µg/kg (i.e., 0.000625 mg/kg), 1.25 µg/kg, and 2.5 µg/kg.

EX2070 (NCT03144271), 6; EX2010 (Rosenstock Decl.), ¶227; POR.24

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

- **WO421** also discloses GLP-1 agonists dosed in increments ***twenty times smaller than 0.1 mg*** (e.g., 5µg (0.005mg)).
- GLP-1 agonists exenatide and lixisenatide are 5/10µg and 10/15/20µg, respectively.

EX1011 (WO421), 43:1-19;
EX2010 (Rosenstock Decl.), ¶¶228-229; POR.24

The GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art. For example, exenatide is administered twice daily by subcutaneous injection (Byetta, 5-30 µg, particularly 5-20µg, preferably 5-10 µg, specific dosage strengths are 5 or 10 µg) before a main meal.

Exenatide LAR is administered once weekly by subcutaneous injection (0.1-3 mg, particularly 0.5 mg to 2.0 mg, specific dosage strengths are 0.8 mg or 2.0 mg).

Liraglutide is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg).

Taspoglutide is administered once weekly by subcutaneous injection (1-30 mg, specific dosage strengths are 1 mg, 8 mg, 10 mg, 20 mg or 30 mg).

Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).

Albiglutide is administered once weekly by subcutaneous injection (4-30 mg, specific dosage strengths are 4 mg, 15 mg or 30 mg).

Lixisenatide is administered once daily by subcutaneous injection (10-20 µg, specific dosage strengths are 10 µg, 15 µg or 20 µg).

Dulaglutide is administered once weekly by subcutaneous injection (0.25-3 mg, specific dosage strengths are 0.25 mg, 0.5 mg, 0.75 mg, 1.0 mg, 1.5 mg, 2.0 mg or 3.0 mg).

EX1011 (WO421), 43:1-19

There Is No Basis Other Than Improper Hindsight for Petitioner's Arbitrarily-Declared Dosing Increments (*cont'd*)

- And Petitioner's Dr. Bantle confirmed there were **no data** showing that adjusting semaglutide in an interval less than exactly tenths-of-a-milligram (0.1mg) would **not** impact results.

EX2018 (Bantle Dep. Tr.), 67:5-16, 86:3-11, 101:21-102:6, 107:1-6, 117:14-118:4;
EX2019 (Jusko Dep. Tr.), 17:21-18:21; EX2010 (Rosenstock Decl.), ¶232; POR.25

- Indeed Ozempic® (the active ingredient of which is semaglutide) is actually approved to be administered in doses **0.25mg** once weekly.

EX2069 (Ozempic® 2017 Label), 1; EX2010 (Rosenstock Decl.), ¶238; POR.30

Petitioner's “At Once Envisage” Law Is Inapplicable

- Petitioner asserts the “genus” of “0.1-1.6mg” would be understood as “a disclosure of a discrete and limited class of doses a POSA can at once envisage.”
- But this is wrong because WO421 and Lovshin disclose an enormous, and potentially infinite, number of doses (***at least*** 320 or 3,200)—not a “limited class.”

Pet.30

EX2010 (Rosenstock Decl.), ¶¶219-236; POR.22-28; SurRep.10-14

[D]isclosure of a genus... is not necessarily a disclosure of every [member] species.

Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006); POR.20

Petitioner's “At Once Envisage” Law Is Inapplicable (*cont'd*)

There are an enormous, and potentially infinite, number of such discrete points within the continuous range of 0% to 5% water content taught by V Powder.

Fonterra Co-Operative Grp. Ltd. v. Arla Foods Amba, IPR2022-00661, Pap.15, 10-11 (Aug. 31, 2022); SurRep.10

In re Petering stands for the proposition that a skilled artisan may “at once envisage each member of [a] limited class, even though the skilled person might not at once define in his mind the formal boundaries of the class.” **The key term here is “*limited*.”**

Mylan Pharms. Inc. v. Merck Sharp & Dohme Corp., 50 F.4th 147, 153 (Fed. Cir. 2022)
(citations omitted) (affirming Board's conclusion a known class of 957 salts did **not** anticipate the claimed species); POR.26-27; SurRep.13-14

Petitioner's "At Once Envisage" Law Is Inapplicable (cont'd)

- Petitioner's Dr. Jusko admits dosing in smaller increments was possible for semaglutide:

Q. With respect to the -- what you call the range of doses that were used in the semaglutide trials, **would it have been possible to test doses at intervals of less than 0.1 milligram?**

A. **That possibility exists, but clinical trials have to be reasonable in terms of the number of increments and doses that it's feasible to examine.**

* * *

Q. But you could administer a dose in less than a 0.1 milligram increment to a patient, correct?

A. **By "increment," you mean 8.1 versus 8.0?**

Q. For instance, it would be possible to give a patient 0.27 milligrams of semaglutide, correct?

A. **It's a theoretical possibility, but not a very practical one.**

EX2553 (Jusko Reply Dep. Tr.), 42:6-43:9; SurRep.11

Petitioner's "At Once Envisage" Law Is Inapplicable (*cont'd*)

Petitioner relies on a conclusory statement that “the most preferable oral dosage range for linagliptin [disclosed in the '510 publication] encompasses and thus anticipates the claimed dose recited” in the challenged claims. ... **But, Dr. Davidson does not testify, and Petitioner does not argue, that an ordinary artisan would understand any dosage within the preferred dose of 1 to 100 mg administered “1 to 4 times a day” disclosed in the '510 publication to be efficacious. ... Here, the only evidence Petitioner relies on is a broad range of potential linagliptin dosages.** That does not amount to a preponderance of the evidence. ... **Petitioner does not explain why, based on the disclosure of a genus of dosage ranges for DPP-4 inhibitors, a person of skill in the art would immediately envisage administering linagliptin in the dosage amounts recited** in the challenged claims 14 and 20.

Mylan Pharms. Inc. v. Boehringer Ingelheim Int'l GmbH, IPR2016-01566, Pap.15, 8-9 (Feb. 3, 2017); POR.26-27

Petitioner's “At Once Envisage” Law Is Inapplicable (*cont'd*)

Defendants ask this Court to **transform the range from a set with infinite members to one containing seven**, based on the asserted **selection preferences** of a skilled artisan. ... Defendants’ “narrowing” approach **looks very much like an attempt to rewrite the ’006 patent to create a hindsight anticipation.**

Janssen Pharms. Inc. v. Watson Lab’ys, Inc., No. 08-cv-5103-SRC, 2012 WL 3990221, at *8-9 (D.N.J., Sept. 11, 2012); SurRep.11-12 & n.8

Petitioner's "At Once Envisage" Law Is Inapplicable (*cont'd*)

Thus, the Defendants' anticipation theory involves the POSA arbitrarily and improperly selecting 40 mg/ml from the range of 10-50 mg/ml and cobbling together other, disparate disclosures from Dix '226. But to anticipate, the prior-art reference must disclose each element "arranged as in the claim." The Defendants' "mechanistic dissection and recombination" of disclosures from Dix '226 involves just the kind of impermissible "hindsight anticipation[]" relying on "the guidance of a[] [patentee's] disclosures" that precedent has long forbid.

Following that precedent, the Janssen court rejected an anticipation argument indistinguishable from the one the Defendants raise here, concluding that a dosage range of ".02-0.05 mg" did not anticipate a specific dose of "0.025 mg." The Court's holding in Janssen is consistent with Federal Circuit precedent explaining that where "[t]he disclosure is only that of a range, not a specific [point] in that range, ... the disclosure of a range is no more a disclosure of the end points of the range than it is of each of the intermediate points." The Court holds likewise here that the range of 10-50 mg/ml in Dix '226 does [sic, not] disclose every intermediate point in the range, including 40 mg/ml.

Petitioner's “At Once Envisage” Law Is Inapplicable (*cont'd*)

The Defendants also argue that Regeneron must show criticality of the claimed aflibercept concentration. **However, the Federal Circuit has held that criticality is a factor only where a disclosed range “overlaps” with a “claimed range,” not a specific point.** Furthermore, the Federal Circuit has specifically rejected equating “discrete points” in a range with a range itself. **The Product Patent claims a specific concentration — 40 mg/ml — not a “claimed range.”** The Defendants cite no case where a court considered criticality in an anticipation inquiry under these circumstances.

Regeneron Pharms., Inc. v. Mylan Pharms. Inc., 2024 WL 382945, at *47-49, *74-78 (N.D. W. Va. Jan. 31, 2024) (citations omitted); SurRep.11-12 & n.8

Petitioner's "At Once Envisage" Law Is Inapplicable (*cont'd*)

...Defendants argue that the POSA "would easily envisage" the claimed regimen as one possible regimen that could result from the administration of three loading doses followed by PRN treatment. They focus on the description of one arm of the Phase 2 DA VINCI trial where patients were being treated with 2.0 mg of aflibercept for 3 initial loading doses, followed by PRN treatment.

They rely on *Wm. Wrigley Jr. Co. v. Cadbury Adams USA LLC*, 683 F.3d 1356, 1361 (Fed. Cir. 2012), to argue this disclosure is anticipatory because the POSA "would easily envision the rest of the regimen to include one option with 5 doses, separated by 4 weeks, followed by an 8-week dose interval." In other words, the **Defendants argue it is possible doctors following the regimen described in the Press Release would administer the three monthly loading doses described in the Press Release and then, for a given patient, just so happen to administer injections during the PRN phase** in a pattern that matches that of the claimed regimen—(1) an injection at the first PRN visit, (2) an injection at the second PRN visit, (3) no injection at the third PRN visit, and (4) an injection at the fourth PRN visit. The Defendants argue such a pattern of injections conforms to the claimed regimen because it equates to five monthly doses followed by a dose eight weeks later, as the asserted claims require.

The Court disagrees; **Wrigley is inapposite**. In *Wrigley*, a case about chewing gum containing a combination of WS-23 (a cooling agent) and menthol (a flavoring agent), the prior art reference "list[ed] several categories of components that can be included in the compositions." The Court held that **the reference anticipated because it plainly "envision[ed] using WS-23 and menthol in a single product" and "the number of categories and components in [the] reference was [not] so large that the combination of WS-23 and menthol would not be immediately apparent to one of ordinary skill in the art."** In other words, the limitations of the claims themselves were disclosed in the prior art reference. **That logic does not apply to the September 2009 Press Release, which does not disclose five loading doses and does not disclose various regimen components in a manner it suggests can be mixed and matched; it rather discloses a single regimen—three monthly loading doses followed by PRN dosing—that is not the one claimed.**

Petitioner's Late Attempt to Construe 1.0mg Is Improper and Irrelevant

- Petitioner asserts an unspecified “‘standard scientific convention’ of rounding applies based on a number’s mathematically significant figures.”
Rep.10-11
- But this new, late argument has ***no legal support***.
SurRep.12 n.10
 - In Petitioner’s cited *Viskase Corporation v. American National Can Company*, 261 F.3d 1316, 1322 (Fed. Cir. 2001) the **Federal Circuit reversed** the lower court’s application of “standard scientific convention” based on prosecution, and the term was “***about*** 0.91,” not “0.91.”
SurRep.12 n.10
- And this argument is irrelevant and conflates (1) claim construction and (2) **POSITA’s understanding of WO421**.
SurRep.12 n.10
 - The evidence confirms dosing increments for semaglutide of less than tenths-of-a-milligram would have been meaningful to POSITA.

EX2069 (Ozempic® 2017 Label), 1; EX2070 (NCT03144271), 6; Slides 73-81; SurRep.12 n.10

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin

- Petitioner **cites no case where a broad numerical range anticipated a claimed single, discrete point**, such that criticality even needs to be considered.

SurRep.15, n.11

- But even if reached, the **claimed dose here *is* within a critical range** that is a subset of the prior art range.

EX2010 (Rosenstock Decl.), §VIII.A.4; SurRep.17; *see also* POR.30-35, 39

- Here, the evidence shows the claimed dose operates differently from other portions of the prior art range.

SurRep.14-17; *see also* POR.30-32

A single, discrete point suggests a difference in how the invention operates at another discrete point. A single, discrete point compared to a range disclosed in the cited prior art, thus, presents a situation more analogous to that in *In re Baird*, in which the prior art taught a wide range of chemical compounds and the claims at issue recited a single compound within that range. ... Here, the challenged claims require a specific water content unmodified by “about” or any similar term. There are an enormous, and potentially infinite, number of such discrete points within the continuous range of 0% to 5% water content taught by V Powder.

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin (*cont'd*)

- Even if a **range** could anticipate a **single point/dose** (it does not), a 1.0mg dose would be part of a critical range:

Here, the prior art, JP 51–82250, discloses a temperature range of 100 to 500 °C which is broader than and fully encompasses the specific temperature range claimed in the '514 patent of 330 to 450 °C. **Given the considerable difference between the claimed range and the range in the prior art, no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim.**

Atofina v. Great Lakes Chem. Corp., 441 F.3d 991, 999 (Fed. Cir. 2006); POR.31; SurRep.14-17

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin (*cont'd*)

A correct application of *Atofina* and *ClearValue* to the evidence presented here reveals clear disputed material issues of fact and mandates reversal of the district court's finding of anticipation. OSRAM contends—and presented expert testimony and evidence to support its contention—that the limitation of less than 0.5 torr is central to the invention claimed in the '905 patent and that a lamp would operate differently at various points within the range disclosed in the Anderson '334 patent. Specifically, the patent itself claims that prior lamps, including those disclosed in the Anderson '334 patent, are inefficient and impractical as compared to the '905 lamp precisely because they use pressure well above that claimed in the '905 patent.

OSRAM Sylvania, Inc. v. Am. Induction Techs., Inc., 701 F.3d 698, 705-06 (Fed. Cir. 2012); POR.30-31

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin (*cont'd*)

In *Atofina*, we reversed the district court's finding of anticipation where the patent-in-suit claimed a temperature range that was critical to the operability of the invention and the range disclosed in the prior art was substantially different. *Atofina* involved a patent claiming a method of synthesizing difluoromethane at a temperature between 330–450 °C. *Atofina*'s patent and its prosecution history described the claimed temperature range as critical to the invention, and stated that the synthesis reaction would not operate as claimed at a temperature outside the claimed range. The prior art at issue in *Atofina* disclosed a broad temperature range of 100–500 °C. **The patent-in-suit was not anticipated because there was a “considerable difference” between the prior art’s broad disclosure and the claimed “critical” temperature range**, such that “no reasonable fact finder could conclude that the prior art describes the claimed range with sufficient specificity to anticipate this limitation of the claim.” Key to this conclusion was the fact that the evidence showed that **a person of ordinary skill in the art would have expected the synthesis reaction to operate differently, or not all, outside of the temperature range claimed in the patent-in-suit.**

Ineos USA LLC v. Berry Plastics Corp., 783 F.3d 865, 869 (Fed. Cir. 2015) (citations omitted); SurRep.16; see also POR.28

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin (*cont'd*)

- Drs. Bantle and Jusko both incorrectly required that 1.0mg act differently than **every other dose in the range**.

SurRep.17 n.13

Q. Well, what's your understanding of 'criticality' as you used it to perform your analysis and determine that the 1 milligram dose is not critical?

A. My understanding is that for the dose to be critical, must have greater efficacy or tolerability than other doses.

Q. Than other doses in the prior art range?

A. Yes.

* * *

Q. Okay. And my follow-up question to that is, when you said that the dose has to be -- for the dose to be critical, it must have greater efficacy or tolerability than other doses, did you mean than **all** the other doses in the prior art range?

A. Yes.

EX2552 (Bantle Reply Dep. Tr.), 42:14-43:2, 58:3-59:9; SurRep.15 n.12

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin (*cont'd*)

- Drs. Bantle and Jusko both incorrectly required that 1.0mg act differently than **every other dose in the range**.

SurRep.17 n.13

Q. Sure. With respect to criticality, is it your understanding that the 1 milligram dose had to be different than **every** other dose in the range disclosed in the prior art to be critical?

A. **Yes**, I would....

EX2553 (Jusko Reply Dep. Tr.), 18:19-20:22; SurRep.15 n.12

- Because they both applied the incorrect legal standard, their testimony should be given **no weight**.

EX2552 (Bantle Reply Dep. Tr.), 11:14-13:13, 42:14-43:2, 58:3-59:9;
EX2553 (Jusko Reply Dep. Tr.), 11:11-21, 18:19-20:22, 23:4-24:5; SurRep.15 n.12, 17 n.13

Petitioner's Experts Applied the Wrong Criticality Standard

- Petitioner **erroneously** argued that the critical effect **must be claimed**: “Without any required treatment effect, or lack of side effects, there is no basis for PO’s criticality argument.”

Rep.13-15 (citing *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020)); Slides 27-29, 104-107

- And Drs. Bantle and Jusko also **agreed** that “to be critical, the patent would need to require a specific degree of efficacy or tolerability,” which is wrong

EX2553 (Jusko Reply Dep. Tr.), 11:11-21, 18:19-20:22, 23:4-24:5; EX2552 (Bantle Reply Dep. Tr.), 11:14-13:13, 42:14-43:2, 58:3-59:9; SurRep.15 n.12

Q. In forming your [criticality] opinions, did you assume that the feature **needed to be claimed** in the patent at issue?

A. **Yes.**

EX2552 (Bantle Reply Dep. Tr.), 11:14-13:13, 42:14-43:2, 58:3-59:9; SurRep.15 n.12

Q. And how did you determine that the dose in claim 1 was **not critical**?

A. **Because the patent claim does not require any specific degree of efficacy or tolerability.**

Q. So for the dose in claim 1 to be critical, the **patent would need to require a specific degree of efficacy or tolerability**, based on your understanding. Is that correct?

A. **That’s correct.**

EX2553 (Jusko Reply Dep. Tr.), 11:11-21, 18:19-20:22, 23:4-24:5 (“Q. **So you assumed that those quantitative criteria would need to be listed in the claim, correct?**
A. **That is my belief**”); SurRep.15 n.12

Petitioner's Experts Applied the Wrong Criticality Standard

- But **differences in results from practicing the claimed method** (here, including efficacy and tolerability) **need *not* themselves be *claimed*** to establish criticality.

SurRep.15-16

- **OSRAM's differences in operation**—relating to “practicality”/“[e]fficiency”—**weren't claimed**. Instead the ***specification*** discussed the prior art as “inefficient and impractical,” and the Court nonetheless remanded for ***criticality*** analysis.

701 F.3d at 701 (“The lamps described in the Anderson '334 patent operated with a buffer gas pressure of ‘approximately 1 torr or less.’ The ' 905 patent ***specification describes Anderson's lamp as inefficient and impractical***, however.”), 706; SurRep.15-16;
see also *Ineos, Atofina, and Genentech* (***none*** of which require ***claiming*** the results)

Petitioner's Experts Applied the Wrong Criticality Standard

- Petitioner asserts “there is nothing to suggest that a 1.0 mg dose is critical in any way” and that ‘462’s data “demonstrate[s] semaglutide causes a beneficial treatment effect—a reduction of HbA_{1c} or weight loss—across *all tested doses*.”
Pet.32
- But this is *wrong*: 1.0mg is part of a *critical range* that *works differently than other doses in the prior art range*, including with respect to HbA_{1c} and weight loss, with acceptable tolerability.

EX1001 ('462 Patent), Figs.1-5, 23:5-6; EX2010 (Rosenstock Decl.), ¶¶241-255, 281-285; POR.30-35, 39

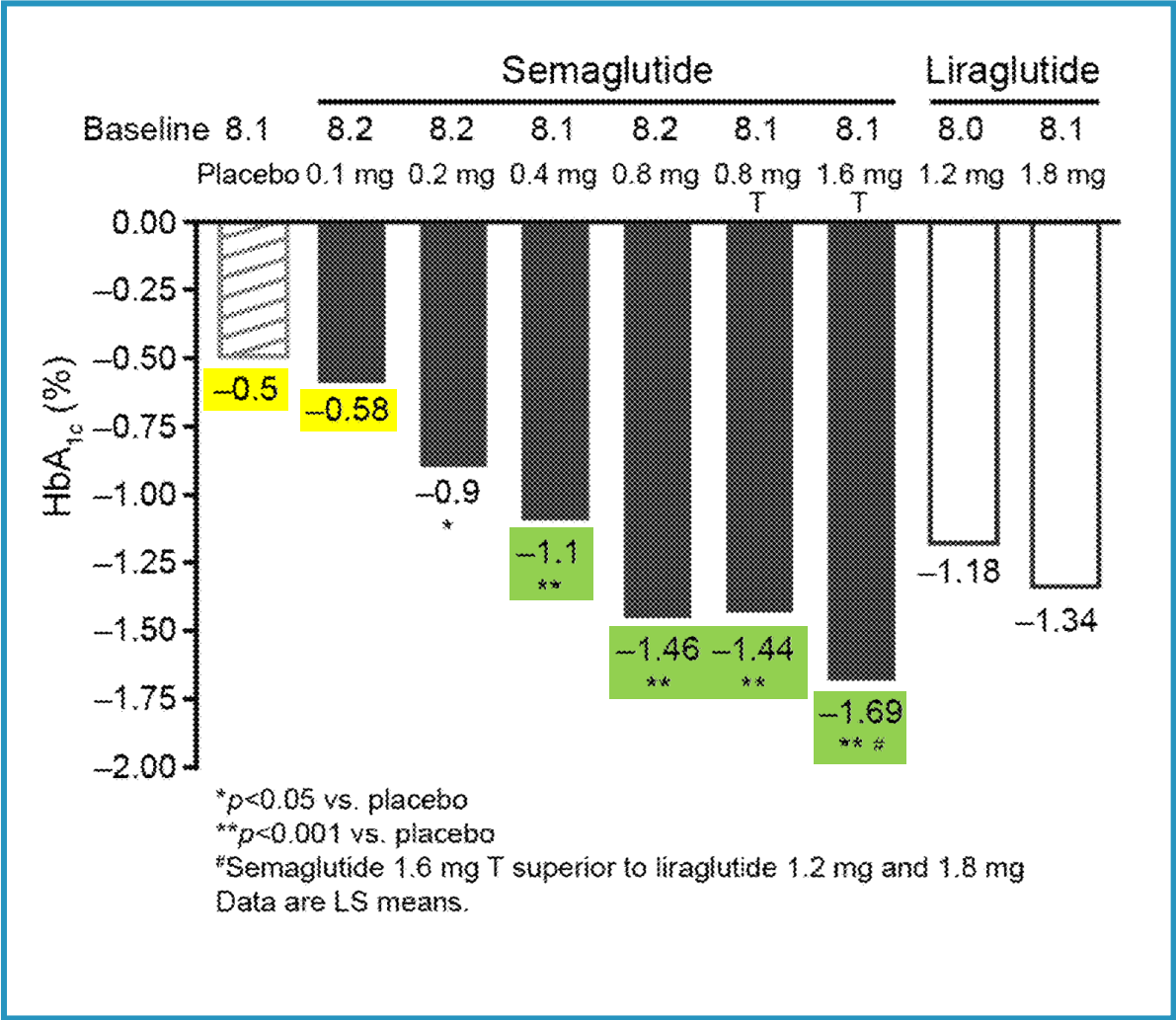
1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin for Reducing HbA_{1c}

- 0.1mg—part of the asserted prior art range—did **not** result in statistically significant improvement in HbA_{1c} reduction over placebo.

EX1001 ('462 Patent), Fig.1; EX2010 (Rosenstock Decl.), ¶¶242, 244, 246-247; POR.32

- In contrast, 0.4mg and up resulted in statistically significant improvement over placebo with a P value of 0.001.

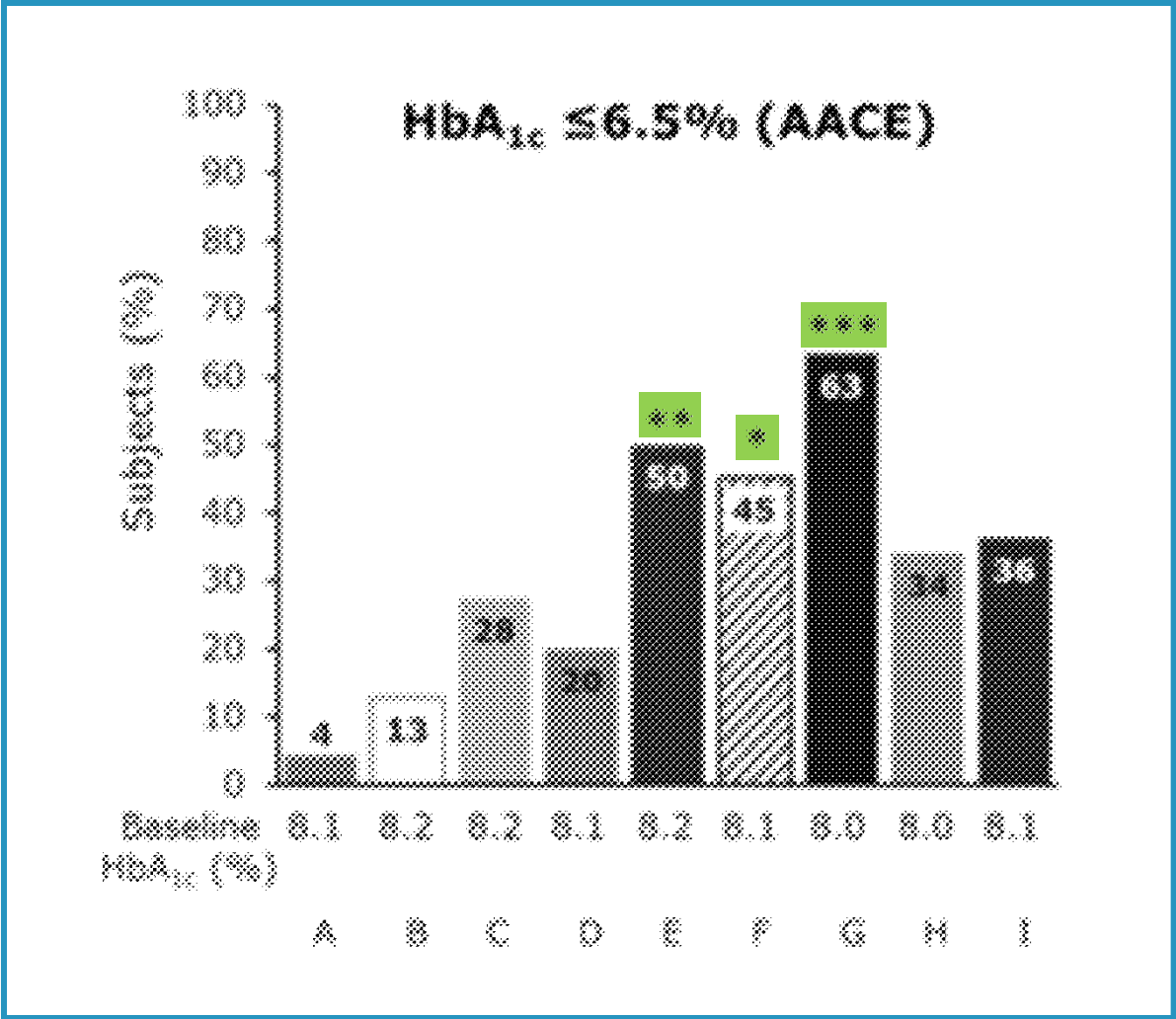
EX1001 ('462 Patent), Fig.1; EX2010 (Rosenstock Decl.), ¶¶242, 244, 246-247; POR.32



1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin for Reducing HbA_{1c} (cont'd)

- And only $\geq 0.8\text{mg}$ brought subjects' HbA_{1c} to the recommended level versus placebo.

EX1001 ('462 Patent), Fig.3A; EX2010 (Rosenstock Decl.), ¶¶242, 244, 246-247; POR.32



1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin for Reducing HbA_{1c} (cont'd)

- The '462's specification consistently distinguishes between results for doses **below** 0.8mg (or 0.7mg) and those **above** it, because **they treat T2D differently**.

EX1001 ('462 Patent), Figs.1-5, 1:31-4:24 (“**at least 0.7 mg**” weekly);
EX2010 (Rosenstock Decl.), ¶¶ 241-255, 281-285; POR.30-35, 39

- The Ozempic® Label instructs physicians to “increase the dosage to 1 mg” “[i]f additional glycemic control is needed”:

.....**DOSAGE AND ADMINISTRATION**.....

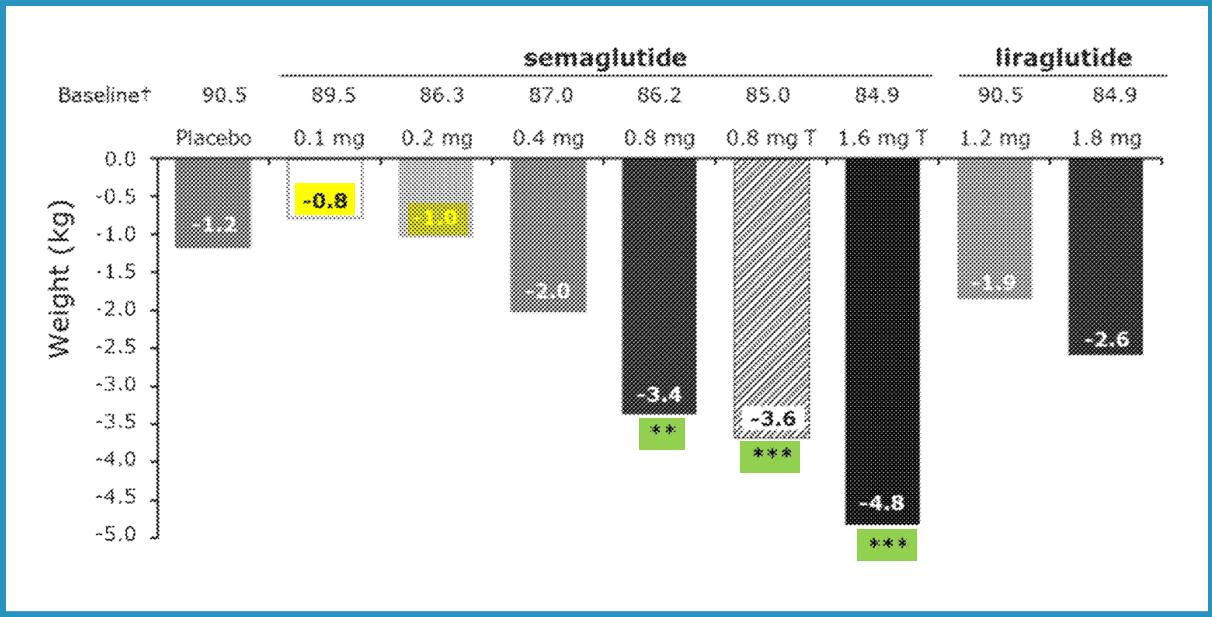
- Administer once weekly at any time of day, with or without meals (2.1).
- Start at 0.25 mg once weekly. After 4 weeks, increase the dosage to 0.5 mg once weekly (2.2).
- **If additional glycemic control is needed, increase the dosage to 1 mg once weekly after at least 4 weeks on the 0.5 mg dose (2.2).**
- If additional glycemic control is needed, increase the dosage to 2 mg once weekly after at least 4 weeks on the 1 mg dosage (2.2)
- If a dose is missed administer within 5 days of missed dose (2.2).
- Inject subcutaneously in the abdomen, thigh, or upper arm (2.2).

EX2069 (Ozempic® 2017 Label), 1

- And as Dr. Goland testified, “**virtually everybody**” moves to 1 milligram.

EX1140 (Goland Dep. Tr.), 29:11-30:20, 34:14-35:16;
EX2069 (Ozempic® 2017 Label), 1; SurRep.17

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin for Reducing Body Weight



EX1001 ('462 Patent), Fig.5; POR.33-34

- 0.1mg, 0.2mg, and 0.4mg—all part of the asserted prior art range—did **not** result in statistically significant weight loss as compared to placebo.

EX1001 ('462 Patent), Fig.5; POR.32

- In contrast, 0.8mg and 1.6mg resulted in statistically significant weight loss over placebo and liraglutide at 1.2mg, and 0.8mg T and 1.6mg T semaglutide caused statistically significant weight loss as compared to liraglutide 1.8mg.

EX1001 ('462 Patent), Fig.5; POR.32

- “The effect of semaglutide 0.4 mg on glycaemic control and body weight was comparable to that of liraglutide 1.2 mg, while semaglutide ≥ 0.8 mg appeared to bring more subjects to target and provided better weight loss than liraglutide 1.8 mg.”

1.0mg Is Within a Critical Part of the Range Disclosed in WO421 and Lovshin for Tolerability

- “Proportion of subjects with **nausea and vomiting increased with dose**, but were generally mild or moderate and ameliorated by titration.”

EX1001 ('462 Patent), 23:5-6; EX2010 (Rosenstock Decl.), ¶¶254-255; POR.34-35, 39

- Dr. Jusko testified that:

[T]he 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. Indeed, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses.

EX1005 (Jusko Decl.), ¶234; EX2018 (Bantle Dep. Tr.), 45:5-16; see also EX2010 (Rosenstock Decl.), ¶¶257-258; POR.34-35, 39

Even If Criticality Required the Effects Be Claimed, “Treating” Does, Indeed, Require an Expectation of Efficacy and Tolerability

- To gain institution, Petitioner told the Board: “The [district court] agreed the patent’s claims are all about ‘intent’ and ‘purpose’ and not any specific level of efficacy, construing the preamble language to mean ‘the claimed administration *is for the purpose of* care and management of a patient Type 2 diabetes’ or ‘*is intended to* care for and manage a patient with Type 2 diabetes.”

Pap.7 (Petitioner’s Reply to POPR), 1-2 (emphasis original); Slides 6, 27-29

- Dr. Rosenstock confirmed that treating **requires tolerability** and **efficacy**:

Moreover, it still would have been unknown to POSITA whether any of the doses being tested (which did not even include 1.0mg) would have **tolerability**, **safety**, or **efficacy** issues that would have made them **unsuitable for use in treating type 2 diabetes as required by the claims** of the ’462 patent.

EX2010 (Rosenstock Decl.), ¶1305; POR.45

Even If Criticality Required the Effects Be Claimed, “Treating” Does, Indeed, Require an Expectation of Efficacy and Tolerability

- And Petitioner’s Dr. Jusko agrees treatment **requires *tolerability***:

Q. Is it your understanding of claim 1 that a drug that’s entirely intolerable on a dosing schedule that’s entirely intolerable could meet the treatment requirement of the preamble?

A. **Well, the preamble calls for treating diabetes; it doesn’t specify the tolerance issue.**

Q. So **can you treat diabetes with an intolerable drug?**

A. **Well, you’re getting into the realm where a clinician would be needed to help answer that question. But in my view, if the patient won’t accept treatment, then it’s not a treatment.**

EX2553 (Jusko Reply Dep. Tr.), 14:7-15:4; SurRep.1-2

Even If Criticality Required the Effects Be Claimed, “Treating” Does, Indeed, Require an Expectation of Efficacy and Tolerability (*cont'd*)

- Dr. Jusko further testified treatment **requires *clinically meaningful improvement***.

SurRep.1-2

Q. Okay. But in terms of your understanding of what the claim construction of the preamble means, would claim 1 be met if administering the semaglutide as claimed resulted in a statistically insignificant decrease in HbA1c?

A. **Probably not.**

Q. And why is that?

A. **Statistical significance is often a very small change that may or may not correspond to clinical significance. But treating diabetes requires clinically meaningful change.**

EX2553 (Jusko Reply Dep. Tr.), 41:3-15; SurRep.1-2

Even If Criticality Required the Effects Be Claimed, “Treating” Does, Indeed, Require an Expectation of Efficacy and Tolerability (*cont'd*)

- Petitioner’s Dr. Spiegel also agrees treatment **requires *efficacy* and *tolerability***.

SurRep.1-2

Q. So in your opinion, what is -- what does it mean to treat type 2 diabetes with semaglutide?
What is required for it to be a treatment of type 2 diabetes?

A. **What’s required is that there be an acceptable safety and tolerability profile -- and this is not reflected in the patent, this is me, as a physician -- and that it be effective at a given dose and a given frequency of administration in lowering the hemoglobin A1c.**

EX2556 (Spiegel Reply Dep. Tr.), 88:8-18; SurRep.1-2

Criticality Does Not Require That Other Doses in the Range Be “Unworkable” or Inoperable

- Petitioner asserts that criticality requires the difference be “critical to the operability of the claimed invention.”
Rep.14-15 (citing *Genentech, Inc. v. Hospira, Inc.*, 946 F.3d 1333, 1338 (Fed. Cir. 2020); Pet.34)
- But only ***part*** of the prior-art range must work differently or be inoperable for a range subset to be critical.
Slides 90-98; POR.30 n.16; SurRep.16
- And the ranges in WO421 and Lovshin **include values that do not satisfy the claim’s “treating” limitation.**
 - 0.1mg: no efficacy beyond placebo
 - 1.6mg: per Dr. Jusko, expected to not be tolerable

Slides 99, 103, 105

Claim 3 (Grounds 1-2) Additionally Fails Because Neither WO421 Nor Lovshin Inherently Discloses a “Solution”

- The Petition argued **inherency**, asserting that “POSAs knew that a subcutaneous injection is... **necessarily** a solution.”
Pet.35-36, 38
- But subcutaneous injections also include “suspensions,” and therefore Petitioner’s inherency theory **fails**.

EX2004 (Miller), 2; POR.36; *Transclean Corp. v. Bridgewood Servs.*, 290 F.3d 1364, 1373 (Fed. Cir. 2002)
 (“anticipation by inherent disclosure is appropriate only when the reference discloses prior art that must *necessarily* include the unstated limitation”)
 (emphasis original)

- Contrary to Petitioner’s unsupported criticism that “the ‘relatively few examples’ of injectable suspensions required a large needle **inappropriate for humans**,” Bydureon is an FDA-approved suspension **for humans**.

Rep.17; EX2010 (Rosenstock Decl.), ¶418; EX2420 (Bydureon Label), 1; SurRep.19

Petitioner's New Claim 3 Reply Theory (for Ground 1 only) Is Improper and Fails

- Petitioner newly asserts on Reply that, for Ground 1, EX2004's "focus on cows, big needles, and suspended crystals underscores POSAs' understanding that the injected doses taught by WO421 were solutions" and that "WO421 expressly refers to 'injectable solutions.'"

Rep.16-17

- But Petitioner's **new "express[]" disclosure theory is prohibited**, as is Petitioner's reliance on new evidence.

SurRep.18-19 & n.14

- "Rather than explaining *how its original petition was correct*, [petitioner argued] an ***entirely new theory of prima facie obviousness absent from the petition.***"

Wasica Finance GmbH v. Cont'l Auto. Sys., Inc., 853 F.3d 1272, 1286 (Fed. Cir. 2017); see also *Intelligent Bio-Sys v. Illumina Cambridge Ltd.*, 821 F.3d 1362, 1369-70 (Fed. Cir. 2016) (affirming rejection of new theory referencing new evidence);

In re NuVasive, Inc., 841 F.3d 966, 971-973 (Fed. Cir. 2016) (vacating/remanding where Board relied on prior-art figure first argued in reply);

POR.35-36; SurRep.18 & n.14

- Even if considered, Petitioner's new evidence confirms its actual Petition inherency theory **fails**.

- Petitioner omits from its new WO421 evidence that the subcutaneous injection may be a suspension: **"Injectable formulations of the GLP-1 receptor agonists of this invention may be... injectable solutions or *suspensions*."**

EX1011 (WO421), 39:20-26; SurRep.19

- This confirms WO421 does **not** inherently disclose a **solution**, and the Petition's inherency theory fails.

POR.35-36; SurRep.18-19

Ground 2, Claim 3: Petitioner's Reply Does Not Respond to PO's Inherency Arguments for Petitioner's Lovshin Ground (Ground 2)

- The Reply **never responds** to the POR's arguments that **Lovshin** does not inherently disclose "a solution."
- Petitioner's improper new reply theory for WO421, even if considered, is inapplicable to Lovshin.

POR.40; Rep.17-19; SurRep.18-19

Slide 110

Ground 2: Lovshin Does Not Disclose Administering Semaglutide to “a subject in need thereof”

- Petitioner’s only Lovshin citations are to Table 1 and to Lovshin being “under active clinical investigation in phase I-II studies.”

Pet.36-37

- But Petitioner cannot rely on semaglutide’s Phase I and II studies for this limitation.

POR.39-40

- **NCT773** is the only alleged prior-art Phase I semaglutide study, and it **excluded T2D patients**.

EX1014 (NCT773), 11-12; POR.39-40

- To the extent Petitioner and its experts were referring to **NCT657**, it is **impermissible to fill in a missing limitation for anticipation by looking to another reference**.

Studiengesellschaft Kohle, m.b.H. v. Dart Indus., Inc., 726 F.2d 724, 726-27 (Fed. Cir. 1984); POR.40

- And even if NCT657 were properly considered for this purpose, **1.0mg was not administered**.

EX1013 (NCT657), 7-8; EX2010 (Rosenstock Decl.), ¶287; POR.40

Ground 2: Lovshin Does Not Disclose Administering Semaglutide to “a subject in need thereof” (*cont’d*)

- And Dr. Bantle’s reliance on ***other GLP-1 analogues*** being administered to T2D patients cannot satisfy administering ***semaglutide*** to a subject in need thereof.
EX1003 (Bantle Decl.), ¶307; EX2010 (Rosenstock Decl.), ¶¶288-290; POR.40
- On Reply, Petitioner newly points to the “***title*** of Lovshin” as “Incretin-based therapies for type 2 diabetes mellitus,” and argues that “Lovshin taught T2D treatment with semaglutide” because it “referr[ed] to NN9535 (semaglutide) as an incretin treatment being investigated at ‘0.1-1.6 mg once weekly.’”
Rep.18-19; EX1012 (Lovshin), 1, 2 (Table 1)
- But Lovshin’s reference to NN9535 “as an incretin treatment” **does not disclose *treating* T2D with the required expectation of **efficacy** and **tolerability**, let alone at any particular dose.**

Slides 27-29, 104-107; SurRep.19

Petitioner's Grounds 3-5 Fail

Galderma Is Inapplicable—No Presumption Applies

- Petitioner cites *Galderma* to argue that obviousness here must be assumed and can only be rebutted by secondary indicia.

Galderma Lab'ys, L.P. v. Tolmar, Inc., 737 F.3d 731, 737-38 (Fed. Cir. 2013); Pet.38; Rep.19

- The claim here is directed to a ***single dose*** (1.0mg) – ***not a range***.

POR.31; SurRep.20

- And a claimed “single, discrete point suggests a ***difference*** in how the invention operates at another discrete point.”

Fonterra Co-Operative Grp. Ltd. v. Arla Foods Amba, IPR2022-00661, Pap.15, 10-11 (Aug. 31, 2022); SurRep.20; see also POR.31

Galderma Is Inapplicable—No Presumption Applies (*cont'd*)

- *Galderma's* presumption *also* does not apply because
 - A claimed single, discrete point is not just “somewhat narrower” than the prior art range.

Fonterra Co-Operative Grp. Ltd. v. Arla Foods Amba, IPR2022-00661, Pap.15, 15 (Aug. 31, 2022)
(distinguishing *In re Peterson*, 315 F.3d 1325 (Fed. Cir. 2003); SurRep.20

- The prior art did not demonstrate that the disclosed range was “effective... and well tolerated.”

Galderma Lab'ys, L.P. v. Tolmar, Inc., 737 F.3d 731, 734, 736 (Fed. Cir. 2013); Slides 80, 99, 103, 124-128, 130-134; SurRep.20

- Even if *Galderma's* “presumption” were to apply, it would be rebutted “by showing criticality” or objective indicia—and here PO established both.

Genentech, Inc. v. Hospira, Inc., 946 F.3d 1333, 1341 (Fed. Cir. 2020); SurRep.20; Slides 90-108, 145-211

Petitioner Failed to Establish POSITA Would Have Been Motivated to Try Anything but the Specific Doses Tested in NCT657

- The parties agree POSITA would have looked to NCT657 and NCT773 to understand WO421 and Lovshin, and would have known certain specific doses were tested—***but not 1.0mg***.

Slides 11-13, 69-72; POR.42-43

- But Petitioner provides **no reason to select a different dose than those tested**, particularly given Petitioner's assertion that POSITA would have ***known*** these doses (0.1, 0.2, 0.4, 0.8, and “1.2”/1.6) were safe and effective.

Pet.39-40; EX1003 (Bantle Decl.), ¶400; EX1005 (Jusko Decl.), ¶228; POR.43-44

- And **if motivated to pursue any dose**, it would have been **one of the doses** that was **actually tested**.

EX2010 (Rosenstock Decl.), ¶¶299-300; POR.43

Dose Optimization Is Inapplicable and Fails

- Petitioner argues “selecting a 1.0 mg dose is merely a routine... optimization....”

Pet.44, 39-40; Rep.20

- But dose **optimization** requires the claimed value be **optimized**.

SNF S.A. v. Solenis Technologies, L.P., IPR2020-01730, Pap.10, 16-19 (Apr. 22, 2021) (evaluating whether optimization would lead to the claimed value);

In re Ethicon, Inc., 844 F.3d 1344, 1350-51 (Fed. Cir. 2017) (stating the ratio “achieves the optimal combination...”);

POR.49; Sur-Rep.21-23

- And Petitioner’s experts admit they **did not determine whether 1.0mg once weekly is optimized**.

EX2552 (Bantle Reply Dep. Tr.), 46:18-47:2; EX2553 (Jusko Reply Dep. Tr.), 25:6-27:10, 28:10-29:18;

see also POR.49; EX2018 (Bantle Dep. Tr.), 108:16-109:15; SurRep.21-23

Dose Optimization Is Inapplicable and Fails (*cont'd*)

Q. Would all of those doses have been optimized?

A. **I don't have an opinion about what dose is optimal. I simply have an opinion about what dose is obvious. And clearly, the 1.0 milligram dose was obvious.**

EX2552 (Bantle Reply Dep. Tr.), 46:18-47:2; SurRep.21

Q. And in your report, do you provide the opinion that 1 milligram is the optimal dose?

A. **I do not claim it as the optimum dose. It is a possible optimum dose. But 0.8, 0.9, 1.1 are also feasible.**

* * *

Q. Did you look at any efficacy and tolerability data to determine whether 1 milligram is an optimal dose?

A. **No, I did not.**

EX2553 (Jusko Reply Dep. Tr.), 25:6-27:10, 28:10-29:18; SurRep.21

Rather Than Optimizing, Petitioner's Expert Simply Argues 1.0mg Is “A Nice Round Number”

- Instead, Petitioner's expert said “a **nice round number like 1.0** is wonderful. It's just right there waiting to be selected.”

EX2019 (Jusko Dep. Tr.), 123:19-124:12, 46:19-47:10, 48:7-22, 52:9-18; *see also id.* 79:7-80:1; EX2553 (Jusko Reply Dep. Tr.), 25:19 (“1 milligram is a nice round number”); POR.50; SurRep.11-12

Q. Why not 1.1?

A. In general, **companies and clinicians like to have nice round numbers**. 1.1 might have worked, but 1.0 is such a convenient number, easy to remember.

EX2019 (Jusko Dep. Tr.), 46:19-47:10; POR.50

Q. In concluding that the claimed 1-milligram once-weekly dose of semaglutide for treating Type 2 diabetes would have been obvious to a person of ordinary skill, did you take into account convenience as part of your analysis?

A. Let's say it was in my thoughts and my additional thinking that everybody would recognize that **nice round numbers are ideal when dealing with taking drugs**.

EX2019 (Jusko Dep. Tr.), 52:9-18; POR.50

Dose Optimization Is Inapplicable and Fails (*cont'd*)

[F]or the optimization of a dosage within an established range to be obvious, the asserted prior art must teach that such an established effective range was known.

Mylan Pharms. Inc. v. Biogen MA Inc., IPR2018-01403, Pap.98, 16-17 (Feb.5, 2020) (vacated as moot); POR.46; SurRep.23-24

- But here, Petitioner has not shown that an established effective range was known, let alone that 0.1mg was the bottom end of the range or 1.6mg (WO421 or Lovshin (Ground 3-4)) or “1.2mg” (NCT773 (Ground 5)) was the upper end of the range.

EX2018 (Bantle Dep. Tr.), 80:22-81:9, 107:1-6, 108:16-109:15, 110:11-15, 117:16-118:4;
EX1005 (Jusko Decl.), ¶168 (“Phase II studies define the minimally effective or non-effective dose...”), ¶164;
EX2010 (Rosenstock Decl.), ¶¶119-122, 300-309, 311, 323, 347; POR.44-45, 48-49, 60-63; SurRep.23-24

Q. Would you agree with me that, prior to the '462, there were no results available in the art for semaglutide once weekly at any dose; correct?

A. **There was no data available. I would agree with that.**

EX2018 (Bantle Dep. Tr.), 107:1-6; POR.48, 72

Dose Optimization Is Inapplicable and Fails (*cont'd*)

- Per Dr. Bantle:

Q. Would it be your expectation that a 1.2-milligram dose would be more effective than a .8-milligram dose?

A. I would not necessarily assume that. I think as we get to the higher doses, .8 and above, we may be getting to the maximal effective doses, where an increment in dose doesn't produce much additional benefit. But one would not know that, but I think that would be a reasonable assumption.

EX2018 (Bantle Dep. Tr.), 80:22-81:9; POR.44-45

- Per Dr. Rosenstock:

[T]he existence of trials designed to explore safety, tolerability, and efficacy confirms [] that those had not yet been established. ... As Dr. Bantle and Dr. Jusko do not dispute, prior to the '462 patent there was no known data showing semaglutide was safe, effective, and tolerable at any dose, let alone 1.0 mg. Without any such data, it is my opinion that POSITA would not have been motivated to pursue 1.0 mg semaglutide once weekly for the treatment of type 2 diabetes.

EX2010 (Rosenstock Decl.), ¶¶302, 306; POR.43-45

No Motivation Based on Supposedly “Narrow and Finite Range of Efficacious Doses”

- Petitioner argues motivation based on the “narrow and finite range of efficacious doses (16 options at most) in the prior art.”

Pet.40, 47

- But there was **no known “narrow and finite range of efficacious doses.”**

POR.45-46 (citing Pet.40); see *Intelligent Bio-Sys*, 821 F.3d at 1367-69

- There were **not only 16 doses to try.**

Slides 73-89; POR.45; SurRep.10-14

- And the **range was not known to be efficacious.**

Slides 80, 124-128, 130-134; SurRep.23-24

Petitioner's Dose Response Curve Arguments Fail

- Petitioner argues POSITA would have had REOS because they would have known **liraglutide** would provide a consistent dose-response profile, and that **semaglutide** would've followed liraglutide's dose-response profile.

Pet.40 (Citing EX1003 (Bantle Decl.), ¶402; EX1005 (Jusko Decl.), ¶¶85-88, 238

- But at the same time, Petitioner asserts the ***purpose*** of the Phase II study (as in Lovshin and NCT657) would have been ***to determine semaglutide's dose response curve.***

Pet.43

- And Petitioner simply **assumed** 0.8-1.6mg would be at the upper end of its dosing range where the (unknown) dose-response curve plateaued.

Pet.43; EX2018 (Bantle Dep. Tr.), 83:7-21, 86:8-11, 109:16-110:3; POR.44-45, 63-66; SurRep.23-24

Petitioner's Dose Response Curve Arguments Fail (*cont'd*)

- Petitioner's Dr. Bantle admitted that, in fact, "We don't know."

Q. And why is it -- you said, "As you get to the higher doses of .8 and above that you may be getting to the maximal effective doses." How do you know that cutoff for maybe getting to the maximal effective doses is at .8?

A. Well, I don't know that. And we don't have a dose response curve for semaglutide. But it's a drug, like others, that would have a curve where an increment in dose produces an increase in benefit up to a point where it starts to plateau. And at that point, an increase in dose doesn't have much additional benefit. And you don't want to go out onto that plateau because you'll have more side effects without much benefit. So it could be that we've approached that point. We don't know.

EX2018 (Bantle Dep. Tr.), 83:7-21; POR.63-66

Petitioner's Assumption That Semaglutide Would Be Safe, Effective, and Tolerable Based Solely on It Being in Phase II Trials Is Unfounded

- Petitioner asserts “there must have been data-supported scientific rationale for those doses being both safe and efficacious at the tested ranges.”
- But it is undisputed there was no public safety or efficacy data for semaglutide **at any dose**.

Pet.39-40, 42

EX2554 (Coca Dep. Tr.), 105:7-106:19; EX2010 (Rosenstock Decl.), ¶¶357-358; Rep.28; POR.63-66; SurRep.23-25

Far from demands for data, these statements reflect the Board's recognition that **if the prior art had included efficacy data** regarding use of an anti-CGRP antibody to treat vasomotor symptoms, **that fact would have been important in the obviousness analysis, but no such data were disclosed.** The statements also demonstrate that the Board considered whether the references included any other ‘information,’ ‘direction,’ or ‘specific[] suggest[ion]’ that would have led to a reasonable expectation of success.

Eli Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1346-47 (Fed. Cir. 2021); POR.45, 48; SurRep.23

Petitioner's Assumption That Semaglutide Would Be Safe, Effective, and Tolerable Based Solely on It Being in Phase II Trials Is Unfounded (*cont'd*)

- And it is further undisputed that **Phase II trials routinely fail.**

EX2006 (Arrowsmith), 1; EX2010 (Rosenstock Decl.), ¶¶119-122; EX2019 (Jusko Dep. Tr.), 120:20-121:2, 71:2-72:2, 112:17-113:1; POR.44

Q. Have you ever had any phase 2 trials fail in the diabetes space?

A. Not that I'm personally familiar with. But the more generic question is, do phase 2 trials ever fail. And I would have to answer, yes. By definition, it's not yet a proven therapy at that stage.

Q. Why do people run them if they know they're going to fail?

A. Again, I come back to the reductio ad absurdum. You know why they run them? In hopes that they'll develop a blockbuster drug that will be successful and advance to phase 3 and then be marketed and be extremely successful. Recognizing that so many will fail potentially, but what you have to understand it that you can't get to the point of marketing without going through these stages. That's at least the way the drug approval process works. So that's my understanding.

EX2556 (Spiegel Dep. Tr.), 139:1-140:7; SurRep.23-24

- For example, taspoglutide failed after reaching Phase III because it **had unacceptable adverse effects as administered in that trial.**

EX2060 (The Fate of Taspoglutide), 1 (“the taspoglutide phase 3 clinical trials were terminated because of a significantly increased rate of unwanted adverse events.”); EX2010 (Rosenstock Decl.), ¶¶87-93, 149-156, 194-195; EX2018 (Bantle Dep. Tr.), 96:5-12 (not aware taspoglutide failed); EX2019 (Jusko Dep. Tr.), 67:19-68:11 (Petitioner's Dr. Jusko “not surprised” “Phase III trials of taspoglutide were terminated and development of the drug was abandoned due to unacceptable levels of nausea and vomiting” because “that's a class effect of these drugs”); POR.7, 61; Rep.28-29; SurRep.24

Petitioner's Assumption That Semaglutide Would Be Safe, Effective, and Tolerable Based Solely on It Being in Phase II Trials Is Unfounded (*cont'd*)

Although we have rejected the idea that “efficacy data [are] always required for a reasonable expectation of success,” *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1385 (Fed. Cir. 2019) ... **we are hesitant to conclude as a general matter that the disclosure of a Phase II clinical trial plan, standing alone, provides an expectation of success sufficient to render obvious a dosage that was not included within the planned clinical trial.**

Salix Pharms., Ltd. v. Norwich Pharms. Inc., 98 F.4th 1056, 1062-63 (Fed. Cir. 2024); SurRep.23

Indeed, Numerous Cases Have Found *Lack* of REOS After Publication of the Fact That Clinical Trials Were Ongoing

- In *Sanofi*, the Federal Circuit affirmed the district court's conclusion of **no REOS** where a prior art article disclosed “the rationale and design of the... study” testing the drug at issue in the relevant population and stated that it was “expected that treatment” would work because this was “**nothing more than a statement of the hypothesis being tested**” and POSITA “would have been **at best cautiously optimistic**” that the drug at issue would have been effective in the relevant population”

Sanofi v. Watson Lab'ys Inc., 875 F.3d 636, 641-42, 647-50 (Fed. Cir. 2017). POR.55-56, 59-60

- In *Eli Lilly*, the Federal Circuit affirmed the Board's conclusion that there was **no REOS despite** the existence of **published rat data**, where the Board considered as part of its overall obviousness analysis that “**both [references] lacked efficacy data.**”

Eli Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1346-47 (Fed. Cir. 2021); POR.55-56; SurRep.23

Indeed, Numerous Cases Have Found *Lack* of REOS After Publication of the Fact That Clinical Trials Were Ongoing (*cont'd*)

- In *Miltenyi*, Petitioner **failed to establish REOS** based on in vitro experiments and the “**mere existence of a clinical trial, [] absent any of the ‘clinical (human) data or preclinical (animal) data[.]’**” In view of this lack of evidence, and “[c]onsidering the inherent unpredictability of the field and the history of failures of similar technology” the Board did not find REOS.

Miltenyi Biomedicine GmbH v. Tr. of the Univ. of Pa., IPR2022-00853, Pap.11 (Oct. 11, 2022); POR.60

NCT657's and NCT773's Dosing Schemes Did Not Suggest a Purported “Sweet Spot”

- Petitioner argues REOS because the “dosing schemes [] 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.”

Rep.26; EX1300 (Bantle Reply Decl.), ¶¶295-311; EX1301 (Jusko Reply Decl.), ¶¶285-287, 297-298

- This entirely ignores that **Phase II trials routinely fail** and that there were no data about 0.8mg semaglutide (or any other dose) in the prior art.

Slide 127; EX2006 (Arrowsmith), 1; EX2010 (Rosenstock Decl.), ¶¶119-122; EX2019 (Jusko Dep. Tr.), 120:20-121:2, 71:2-72:2, 112:17-113:1; POR.44; SurRep.24

- It also ignores NCT773's top dose being reduced to “1.2” mg (from 1.6mg) would have been understood to be related to potential Japanese-population specific rationales.

Slides 14-16; EX1038 (Seino), 1-2 (“it is well established that the pathophysiology of [T2D] differs between Japanese and Caucasian patients.”); EX2010 (Rosenstock Decl.), ¶¶167-171, 409, 411; EX2019 (Jusko Dep. Tr.), 38:12-20, 39:6-19; POR.77-78; SurRep.24-25

- For liraglutide, the 0.9mg once-daily dose (rather than the 1.8mg approved maintenance dose in the United States) was the highest dose tested in Japanese subjects.

EX1038 (Seino), 1-2; EX2010 (Rosenstock Decl.), ¶¶167-171; POR.77

Petitioner and Its Experts Ignored PO's Statement That Semaglutide Was "On Hold"

- Moreover, **PO announced** that the **semaglutide program was "on hold" and "postponed"** after NCT657 and NCT773 were completed—but, despite this announcement being made in Petitioner's own exhibit, ***Petitioner's experts ignored it.***

EX1035 (Lund), Table 1, 7-8; EX2018 (Bantle Dep. Tr.), 97:15-19; EX2019 (Jusko Dep. Tr.), 122:6-15; EX2065 (Novo Nordisk Annual Report), 26, 111; EX2010 (Rosenstock Decl.), ¶374; POR.67-69 & n.38

- Dr. Bantle was not aware of this statement:

Q. Are you aware that -- are you aware of statements about the development of semaglutide being placed on hold in the 2010 to 2011 time frame after Phase II trials were completed?

A. **I'm not aware of such statements.**

- Dr. Jusko did not address this statement:

EX2018 (Bantle Dep. Tr.), 97:15-19

Q. Did you address anywhere in your declaration the fact that during the 2010 to 2011 time frame, development of semaglutide was placed on hold?

A. **That's in one of the publications, so I was aware something like that was said.**

Q. **Did you discuss that in your declaration at all?**

A. **No. That being designated on hold does not mean much to me.**

EX2019 (Jusko Dep. Tr.), 122:6-15

Petitioner and Its Experts Ignored PO's Statement That Semaglutide Was "On Hold" (*cont'd*)

- Petitioner's attempt to spin this statement fails—delaying Phase III trials by over a year is not a basis to conclude the Phase II trial was a success.

EX2556 (Spiegel Dep. Tr.), 106:22-108:2; EX2552 (Bantle Reply Dep. Tr.), 22:8-16; SurRep.25-26

Q. So in your opinion, a POSA would have assumed that Novo waited years to get the liraglutide long-acting results, even though the semaglutide results would have been assumed to be very favorable by a POSA. Is that correct?

A. Well, I can't speak to Novo Nordisk and its intent. But it would appear so.

EX2552 (Bantle Reply Dep. Tr.), 22:8-16; SurRep.25-26

Petitioner's Reply Newly Asserts Semaglutide's Efficacy Was Known Because of a 2009 Statement Made in PO's 6-K

- Petitioner's Reply first makes a late assertion that Novo announced the Phase II semaglutide trial “demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide.”

Rep.25; EX1282 (Novo 2009 6-K), 12; EX1300 (Bantle Reply Decl.), ¶¶106-112; EX1301 (Jusko Reply Decl.), ¶¶116-128
- But even if considered, this report **says nothing** about **which** semaglutide dose(s) worked or were tolerable or aligned with which liraglutide doses.

EX2552 (Bantle Reply Dep. Tr.), 29:4-33:5-15; SurRep.25-26

Q. For what dose of liraglutide was clinical safety and efficacy broadly in line with semaglutide?

A. That's not stated.

* * *

Q. But there's no way to actually know which dose of semaglutide and which dose of liraglutide were, quote – that had efficacy and safety that were broadly in line, correct?

A. Well, that's not stated. So I have to agree, there's probably no way to know with certainty. But I think it would be – I think a POSA would have known it was probably doses of both medications at the upper end of their dosing ranges.

EX2552 (Bantle Reply Dep. Tr.), 29:4-33:15; SurRep.25-26

There Is No Reasoned Basis to Rely on Liraglutide for REOS

- As support for REOS, Petitioner also asserts “POSAs would also have known that liraglutide, for example, provided a consistent dose-response profile for lower HbA_{1c}, a pattern POSAs would expect semaglutide to follow.”

Pet.40, 19, 51

(“POSAs also knew the upper portion of the range was likely an effective dose, particularly given a POSA’s knowledge of **liraglutide’s** smooth dose-response curve.”), 56-57

- But Petitioner’s experts agreed **structural differences** would be expected to impact both **efficacy** and **tolerability**.

EX2010 (Rosenstock Decl.), ¶¶148, 364-365; POR.64-65; SurRep.24-25

There Is No Reasoned Basis to Rely on Liraglutide for REOS (*cont'd*)

- Per Dr. Jusko:

Q. And in your report, do you recall discussing a variety of GLP-1 analogs?

A. **Indeed so.**

Q. And each of those GLP-1 analogs have structures that differ from the native GLP-1. Is that correct?

A. **I believe so.**

* * *

Q. Do you have an opinion about whether the modifications impact the dosing of the GLP-1 analog?

A. **I've seen the range of doses that are being – were being studied for the analog. So they must impact the dose-response relationship.**

Q. Do you have an opinion about whether the modifications impact the half-life of GLP-1 analog?

A. **The fact that the newer ones were being touted or developed for once-weekly dosing, even once-monthly dosing, means that the half-lives would have been sufficiently long to allow that.**

Q. And the difference in structure impacted the difference in half-life. Is that correct?

A. **That would be so.**

There Is No Reasoned Basis to Rely on Liraglutide for REOS (*cont'd*)

- Per Dr. Spiegel:

Q. Is that because the modifications might in some way impact those intrinsic features?

A. **Yes, absolutely.** The first paper I ever published as a medical student in endocrinology in 1969 described various forms of the related hormone, glucagon, and its ability to signal to increase second messenger, cyclic AMP. And it showed that you could lop off the last two amino acids of this 29 amino acid peptide and still retain some activity. But when you lopped off the last six amino acids, 1 through 23, you abrogated the activity.

By analogy, with GLP-1, 7 to 37 natural peptide, there are modifications that would apparently be tolerable, maybe even beneficial, we can get to that, in pharmacodynamics. **But on the other hand, you could abrogate the effect, and that would, of course, defeat the purpose in terms of using it therapeutically.**

EX2556 (Spiegel Dep. Tr.), 80:12-81:10 (objection omitted); SurRep.25

There Is No Reasoned Basis to Rely on Liraglutide for REOS *(cont'd)*

- Per Dr. Bantle:

Q. Do the modifications made to GLP-1 analogs impact dosing?

A. **Yes, I think so.**

Q. And I think you've said this already, but the modifications made to GLP-1 analogs impact half-life. Is that correct?

A. **Yes, I think that was the intent of the modifications, to prolong half-life.**

Q. And different modifications in different GLP analogs have different half-lives. Is that correct?

A. **Yes, I think so.**

* * *

Q. In your opinion, would an GLP-1 analog that shares these same amino acids be expected to behave in the same way?

A. **No.**

There Is No Reasoned Basis to Rely on Liraglutide for REOS (*cont'd*)

- Indeed, Petitioner's **Dr. Spiegel** admitted there was **insufficient evidence** to establish **at what doses semaglutide would work:**

SurRep.24-25

Q. How do you know which doses will have an effect?

A. You then want to move potentially to animal studies to look at physiologic effects that you're looking for. You, for example, could have a mouse model or rat model with type 2 diabetes and see what the effects are. And so all of these would give you some doses, but ultimately, you wouldn't necessarily be able to extrapolate from those doses to doses in humans. And so this is what phase 1 and phase 2 trials are all about. Phase 1, by the way, primarily safety, going back to that theme. Phase 2 could certainly be looking at pharmacodynamics, pharmacokinetics, and possibly efficacy.

EX2556 (Spiegel Dep. Tr.), 82:2-83:4, 139:1-140:7; SurRep.24-25

There Is No Reasoned Basis to Rely on Liraglutide for REOS (*cont'd*)

- Moreover, both WO421 and Lovshin show **doses vary widely among GLP-1 agonists**—by multiples of between **6,000** and **10,000**.

EX1011 (WO421), 43:4-19; EX1012 (Lovshin), 2 (Table 1); EX2010 (Rosenstock Decl.), ¶1367; POR.65

- But even if liraglutide's dosing could be relied on, POSITA would have expected the **weekly semaglutide** dosing to have been the approved **daily dose** of liraglutide (1.2 or 1.8mg) **times seven** to maintain the same total weekly dose.

EX2010 (Rosenstock Decl.), ¶1368; POR.65-66

Optimization v. Criticality

- Petitioner argues “[e]ven if 1.0mg were optimal for treating T2D, it is not critical...”
- But **not every dose** between 0.1-1.6mg “*treat[s]*” T2D.
- And even if T2D can be treated with certain lower and higher doses, PO has shown 1.0mg is within a critical sub-range of WO421’s or Lovshin’s “range.”

Rep.22

Slides 27-29, 103-107; SurRep.22-23

Slides 90-108; POR.30-35, 39; SurRep.22-23

- *Celltrion, Inc. v. Genentech, Inc.*, IPR2016-01667, Pap.15, 13 (Mar. 2, 2017) (“Nor do we find persuasive the contention by Petitioner and Dr. Boers that the claimed dosage is not critical, as elsewhere they suggest that the recited dosage is an amount effective to provide the intended clinical response.”)

POR.31 n.17

Petitioner's Reliance on “Obvious To Try” in Support of REOS Fails

- Petitioner relies on *In re Copaxone* to argue there was “only a single variable—dose size—from only 16... prior art [doses],” and therefore the “1.0 mg once-weekly dose was, at least, obvious to try.”

In re Copaxone Consol. Cases, 906 F.3d 1013, 1025 (Fed. Cir. 2018); Pet.47

- But “obvious to try” is pertinent to **motivation to combine, *not* REOS**, and Petitioner failed to show there were just 16 doses.

POR.53. *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1357 (Fed. Cir. 2013) (“even if it was obvious to experiment with these options, ‘there is nothing to indicate that a skilled artisan would have had a reasonable expectation that such an experiment would succeed in being therapeutically effective’”); EX2010 (Rosenstock Decl.), ¶1330 (“at least 320” doses in the prior art); POR n.15; SurRep.10-12

Petitioner Fails to Meet Its Burden as to Claims 4-10

- For claims 4-10 (Grounds 3-5), Petitioner **does not attempt** to analyze the scope and content of the prior art, the differences between the claims and the art, motivation to combine, or REOS.

Pet.47-50; *Graham v. John Deere Co.*, 383 U.S. 1 (1966); *OSI Pharms., LLC v. Apotex Inc.*, 939 F.3d 1375, 1382 (Fed. Cir. 2019); EX2010 (Rosenstock Decl.), ¶1384; POR.70

- Ground 3:** Petitioner makes the conclusory assertion that “POSAs were motivated to formulate semaglutide in each of the straightforward manners claims 4-10 recite, and POSAs would have had [REOS] in doing so....”

Pet.48

- The Petition then recites distinct, isolated teachings of the ’424 publication with no explanation as to how or why POSITA would have modified WO421 using those teachings, or whether or how POSITA would have been motivated to make any such modifications with REOS.

Pet.47-50; POR.70

- Petitioner **nowhere even cites WO421** here, and fails to explain why POSITA would have been motivated to use the ’424 publication’s purported disclosures with WO421’s purported disclosures of semaglutide.

POR.70

- Ground 4:** Petitioner merely cites of disparate disclosures scattered across WO537 and fails to show motivation to combine or REOS, just as it failed to do for Ground 3.

Pet.53-54; EX2010 (Rosenstock Decl.), ¶1396; POR.73

- Ground 5:** Petitioner fails to explain whether or how POSITA would have modified NCT657 and/or NCT773 using the ’424 publication, and without providing motivation to combine or REOS explanations.

Pet.58; EX2010 (Rosenstock Decl.), ¶1419; POR.79

Objective Indicia Support the Non-Obviousness of the '462 Patent

Objective Indicia Must Be Considered

Objective indicia “can be ***the most probative evidence of nonobviousness in the record***, and enables the court to **avert the trap of *hindsight***.”

Leo Pharm. Prods., Ltd. v. Rea, 726 F.3d 1346, 1358 (Fed. Cir. 2013); POR.80

The objective indicia of non-obviousness play an important role as a **guard against the statutorily proscribed hindsight reasoning** in the obviousness analysis.

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1328 (Fed. Cir. 2016); POR.81

PO Is Entitled to a Presumption of Nexus Between 1.0mg Once-Weekly Ozempic® and '462

[P]resuming nexus is appropriate “when the patentee shows that the asserted objective evidence is tied to a specific product and that product embodies the claimed features, and is coextensive with them.”

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1373 (Fed. Cir. 2019); POR.80

- **Ozempic®’s label identifies once-weekly subcutaneous 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.**

EX2056 (Sinko Decl.) ¶¶33-68; EX2054 (Goland Decl.) ¶¶39-59; EX2018 (Bantle Dep. Tr.), 129:8-131:14; POR.80-81; SurRep.27-28

PO Is Entitled to a Presumption of Nexus Between 1.0mg Once-Weekly Ozempic® and '462 (*cont'd*)

- To argue against nexus, Petitioner points to:
 - Claim 1 of PO's weight-reduction patent (No. 9,764,003) that **does not** claim treatment of T2D (*left*, below); and
 - PO's **pending patent application** (No. 2019/0134162) that **pertains to cardiovascular outcomes in a different patient population** (*right*, below).

Rep.34-35; EX2002 ('003 Patent), 35:30-35; EX1295 ('162 Pub.), cl. 15

1. A method for reducing body weight, comprising 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, wherein said semaglutide is administered without another therapeutic agent.

EX2002 ('003 Patent), 35:30-34

15. A method of reducing the risk of a major adverse cardiovascular event (MACE), comprising:
administering semaglutide in a therapeutically effective amount to a subject in need thereof, wherein the subject has type 2 diabetes and cardiovascular disease.

EX1295 ('162 Pub.), c. 15

PO Is Entitled to a Presumption of Nexus Between 1.0mg Once-Weekly Ozempic® and '462 (*cont'd*)

- But Petitioner cites no law showing that a pending patent ***application*** is relevant to the question of nexus.
SurRep.27
- Petitioner also erroneously asserts that because PO's evidence relates to unclaimed features—*i.e.*, weight loss, cardiovascular benefits, and kidney benefits—then these features are critical and destroy nexus.
Rep.34-35
 - But these features, although important, do not “materially impact[] the product’s functionality” and become “critical” such that the nexus presumption should not apply.

Fox Factory, Inc. v. SRAM, LLC, 944 F.3d 1366, 1375 (Fed. Cir. 2019); POR.80; SurRep.27-28

PO Has Shown Nexus Even Without a Presumption

- PO has shown a nexus exists even ***without*** a presumption.
 - PO's objective evidence here is tied to 1.0mg once-weekly Ozempic®'s unique characteristics claimed in the '462: (1) administering semaglutide (2) once-weekly at (3) 1.0mg (4) to treat patients with T2D.
- Petitioner **never meaningfully refutes** this demonstration of nexus, instead focusing its attacks exclusively on the presumption.

EX2054 (Goland Decl.), ¶¶46-59, 93; POR.80-81

Rep.36-37; SurRep.28

Petitioner's Attack on Nexus Is Contrary to Law

- Petitioner contends that (as Petitioner argues the prior art) all aspects of the claimed treatment regimen were known except for the specific 1.0mg dosing of semaglutide. Thus, according to Petitioner, all objective indicia evidence must be tied solely to that dosing.

SurRep.28; Rep.36-37, 39, 42

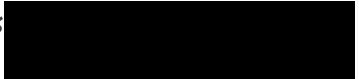
- But even assuming Petitioner's underlying premise, this argument has been expressly rejected by the Federal Circuit: “[c]oncluding otherwise would mean that nexus **could *never* exist** where the claimed invention is a ***unique combination* of known elements from the prior art.**”

Chemours Co. FC, LLC v. Daikin Indus., Ltd., 4 F.4th 1370, 1378 (Fed. Cir. 2021) (citing *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1332 (Fed. Cir. 2016)) (emphases added); SurRep.28

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success

- Ozempic® has unquestionably enjoyed astounding a commercial success.
 - “Demonstrating that an invention has commercial value, that it is commercially successful, weighs in favor of its non-obviousness.”

WBIP, LLC v. Kohler Co., 829 F.3d 1317, 1337 (Fed. Cir. 2016); POR.81

- Across all metrics, Ozempic® has been a “” commercial success.

EX2300 (Velturo Decl.), ¶¶74-76, 77-79, 85-87; POR.81-82

- ***Petitioner’s own experts—Drs. Bantle, Jusko, and McDuff—each agree.***

POR.81; SurRep.28-29; EX2018 (Bantle Dep. Tr.), 123:12-124:3; EX2555 (McDuff Dep. Tr.), 9:15-10:10; EX2019 (Jusko Dep. Tr.), 131:10-132:4

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success *(cont'd)*

Per Petitioner's **Dr. Bantle**:

Q. Okay. Are you aware of what the net sales of Ozempic in the United States were in 2021?

A. **I am not.**

Q. Does 3.4 billion sound familiar for 2021 net sales of Ozempic?

A. **I read somewhere that the sales were 3 billion, and it wasn't clear to me what year or even what country.**

Q. If there were \$3 billion worth of sales in the U.S. in a year, would you say that's commercially successful?

A. **In my opinion, that would be a success.**

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success (*cont'd*)

Per Petitioner's **Dr. McDuff**:

Q. So just to make sure I understand, you're not disputing that Ozempic, as the drug, is a commercial success, right?

A. It depends what you mean by "commercial success." As a secondary consideration, I think it's more complicated. In terms of its product performance, I am not disputing that it has achieved a certain product success overall.

Q. You keep saying "a certain product success." What do you mean by "certain"?

A. Well, "product success" is not very well defined. It depends what you mean by "product success."

Q. Is it your opinion that Ozempic is not successful as a product?

A. I'm not putting it that way.

EX2555 (McDuff Dep. Tr.), 9:15-10:10 ; SurRep.28-29

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success (*cont'd*)

Per Petitioner's **Dr. Jusko:**

Q. ...why would a person of skill in the art have been motivated to develop semaglutide?

* * *

A. **Obviously, it's been a commercial success.**

EX2019 (Jusko Dep. Tr.), 131:10-132:4; POR.81

Per Petitioner's **Dr. Spiegel:**

Q. Semaglutide is so successful that Novo Nordisk can't even supply the consumer demand for it? Is that what I heard you say?

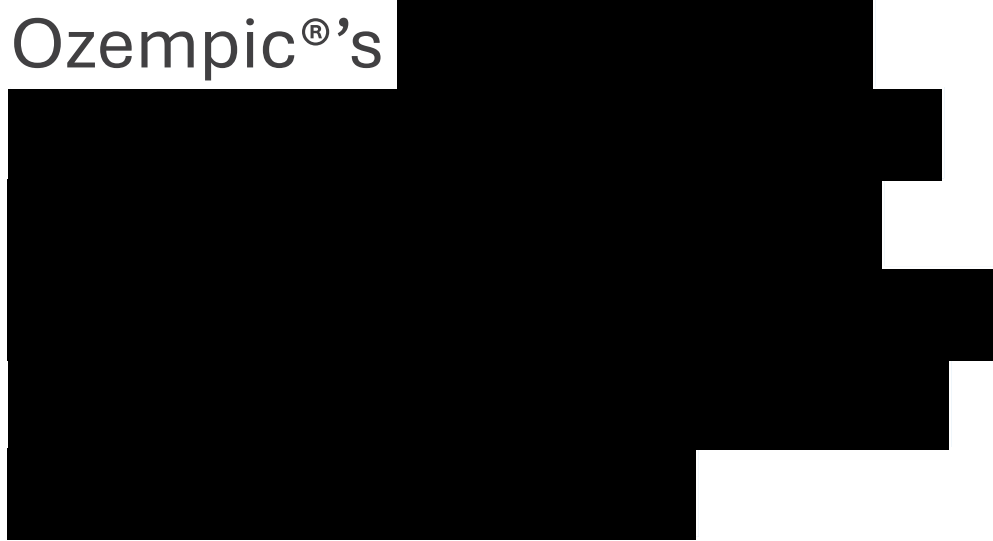
* * *

A. **...if you're asking me about commercial success, yes, undoubtedly.**

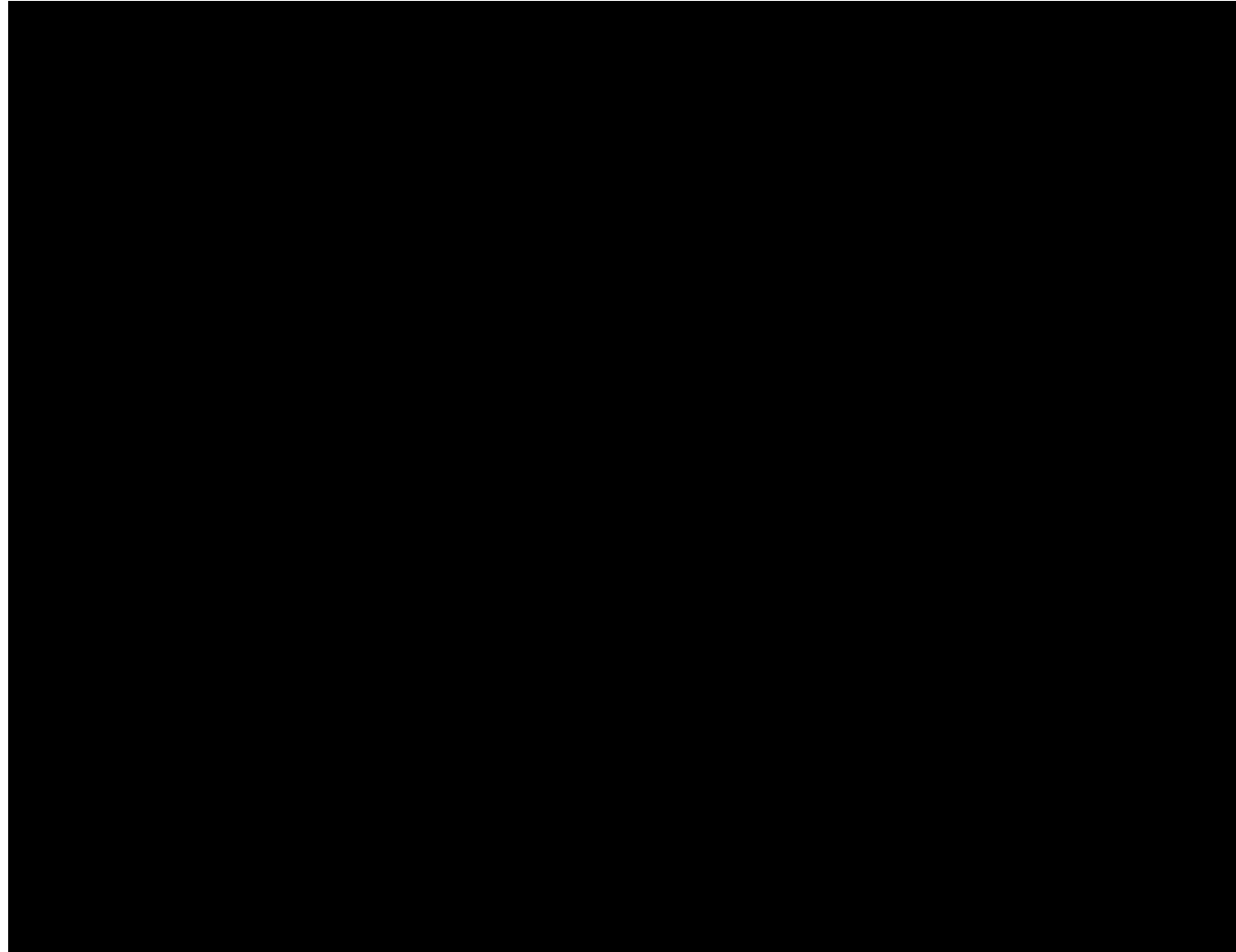
EX2556 (Spiegel Dep. Tr.), 108:3-18; SurRep.29

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Sales

- Ozempic®'s



EX2300 (Velturo Decl.), ¶174 (citing Appx.D, which cites Novo Nordisk Quarterly Reports (EX2494-2516)); POR.81



1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Sales (*cont'd*)

- Ozempic®'s dollar sales overall, both as an absolute number and as compared to other brands—and of the 1.0mg dose specifically—show that 1.0mg once-weekly Ozempic® is a commercial success.

EX2300 (Vellturo Decl.), ¶¶75-76; POR.82

—

[REDACTED]

EX2300 (Vellturo Decl.), ¶85; POR.81

•

[REDACTED]

EX2300 (Vellturo Decl.), ¶75; EX2483 (IQVIA Data); EX2484 (IMS Institute); POR.82

—

[REDACTED]

EX2300 (Vellturo Decl.), ¶85; POR.81; SurRep.28, 30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Prescriptions

-

EX2300 (Velturo Decl.), ¶177; [REDACTED] 7-8; POR.81-82

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Prescriptions (*cont'd*)

-

[REDACTED]

EX2300 (Vellture Decl.), ¶86; POR.81

-

[REDACTED]

EX2300 (Vellture Decl.), ¶86; POR.81

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Marketing

- Marketing for 1.0mg once-weekly Ozempic® focuses substantially on benefits made possible by '462.

- Ozempic®'s promotional messaging emphasize '462's benefits, including [REDACTED]

EX2300 (Velturo Decl.), ¶¶99-101; EX2327 (2021 Quarterly Insights Report), 58-59; EX2322 (2021 Quarterly Insights Report), 56-57; EX2331 (2020 Quarterly Insights Report), 73-74; EX2328 (Specifications for Detailing Material), 4, 6; POR.82

- For example, Ozempic®'s promotional materials highlight [REDACTED]

EX2300 (Velturo Decl.), ¶¶103-104; EX2306 (Brand Strategy Presentation), 32-33; EX2482 ([REDACTED]), 1; EX2331 (2020 Quarterly Insights Report), 60-62; POR.82

- Ozempic®'s promotional materials identify the [REDACTED]

EX2300 (Velturo Decl.), ¶105; EX2328 (Specifications for Detailing Material), 10; EX2334 (Pre-POA Opening Presentation), 137-38; POR.82

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Marketing (cont'd)

- 1.0mg once-weekly Ozempic®'s success is not due to an outsized “advertising campaign.”

Rep.36

—

[REDACTED]

EX2300 (Velturo Decl.), ¶¶106-110; POR.82

—

[REDACTED]

EX2555 (McDuff Dep. Tr.), 59:17-60:2; SurRep.30-31

- Indeed, Petitioner's own cited EX1180—J. David & M. Stewart, *Commercial Success: Economic Principles Applied to Patent Litigation*—belies any contrary argument from Petitioner:
 - Comparative analysis of ratios of promotional spending to sales is a relevant inquiry for the question of commercial success.
 - “[T]he existence of a significant advertising budget does not in itself rebut the presumption that the commercial success of the product at issue must be due to the patented invention.”

EX1180 (David & Stewart), 9; SurRep.30-31

EX1180 (David & Stewart), 11 n.9; SurRep.30-31

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions”

- 1.0mg once-weekly Ozempic®’s success is not due to purported off-label prescriptions.

–

EX2300 (Velturo Decl.), ¶¶88-93; SurRep.29-30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)

—

[REDACTED]

[REDACTED]

EX2300 (Velluro Decl.), ¶91, Appx. I; SurRep.29-30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)

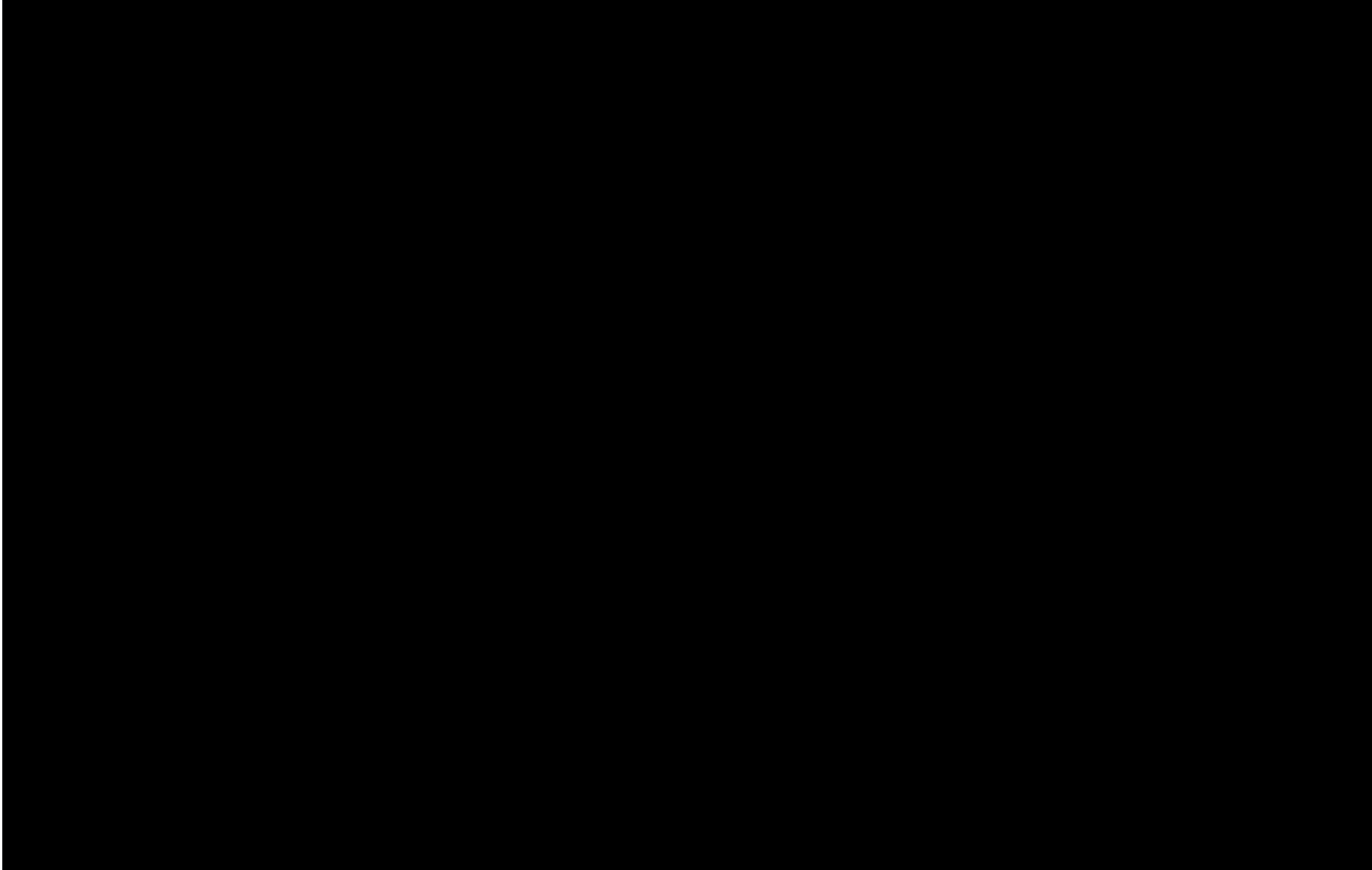
—

[REDACTED]

[REDACTED]

EX2300 (Vellturo Decl.), ¶92, Appx. I; EX2518 (Han); SurRep.29-30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)



1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)

- Petitioner’s expert, Dr. McDuff, on the other hand, principally relies on **non-peer-reviewed newspaper articles** about Ozempic® and other GLP-1 drugs for his opinions that there is significant “off-label” prescribing.

EX1308 (McDuff Decl.), ¶¶53-54; SurRep.29-30

- Dr. McDuff also argued “off-label” use based on a report showing an increase in prescriptions in patients with “a history of **overweight, obesity, and other hyperalimentation.**”

EX1184 (2023 Trends Shaping the Health Economy), 43; EX2555 (McDuff Dep. Tr.), ¶53; SurRep.29-30

- But Dr. McDuff admits **this report never states that the patients it describes *didn’t have T2D*—and thus never shows their use was “off-label.”**

EX2555 (McDuff Dep. Tr.), 29:21-30:6, 31:6-18; EX1184 (2023 Trends Shaping the Health Economy), 43; SurRep.29-30

Q. What percentage of patients that’s included here **does not have type 2 diabetes?**

* * *

A. **I don’t see that figure** here in the study.

EX2555 (McDuff Dep. Tr.), 29:21-30:6, 31:6-18 (omitting witness’s intervening question); SurRep.29-30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)

- Indeed, evidence Dr. McDuff himself cited shows [REDACTED] **of T2D patients are overweight or obese.**

EX2308 (Ozempic® Product Development Plan), 3; SurRep.30

- But Dr. **McDuff was unaware** of this—despite having considered, cited, and relied on this evidence.

EX2555 (McDuff Dep. Tr.), 28:7-10; SurRep.30

Q. What percentage of patients with type 2 diabetes have a history of overweight, obesity, and other hyperalimentation?

* * *

A. **I don't know, sitting here.**

EX2555 (McDuff Dep. Tr.), 28:7-10; SurRep.30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (cont'd)

- Dr. McDuff also drew from a **bar chart** in a **blog post** with **no stated numbers**, as well as a supposed “report” from “**TrackDrugs.com**”—the web site’s one and **only** “report.”

EX1308 (McDuff Decl.), ¶¶53-54; EX1172 (Khan); EX1185 (TrackDrugs); SurRep.30

- But Dr. McDuff **could not explain how the bar chart reliably provided the data:**

Q. The Y axis is labeled with **increments of 2 million**, correct?

A. **Yes**

Q. So looking, for example, at the bar in 2019, just looking at the bar, how are you able to assess that the bar is equivalent to 230,000?

A. **There’s one of two ways. One is doing a proportionality analysis. Sometimes my team does an analysis where you can zoom in on the figure and determine the ratio of the size of the bar to the Y axis to get a best estimate** of what is the number underlying that bar. It’s very **possible** that’s what our team did here....

EX2555 (McDuff Dep. Tr.), 36:12-38:1; SurRep.30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Purported “Off-Label Prescriptions” (*cont'd*)

- And Dr. McDuff admitted that the data underlying the bar chart came from TrackDrugs.com, admitted that he never looked at that underlying data, and that he had no idea what exactly TrackDrugs.com was, who supported it, and whether he had ever used it before.

EX2555 (McDuff Dep. Tr.), 34:4-10, 39:11-41:22, 44:22-46:5; SurRep.30

- Even if, *arguendo*, any of Dr. McDuff’s data could be considered reliable, Dr. McDuff failed to break down any purported off-label usage by dosage, claiming “[i]t wasn’t necessary.”

EX2555 (McDuff Dep. Tr.), 42:12-43:4, 44:9-17; SurRep.30

- This is despite Petitioner’s (unfounded) complaints that PO supposedly didn’t separate commercial success evidence by dosage strength.

Rep.36-37; *cf.* EX2300 (Vellturo Decl.), ¶¶80, 85-93; SurRep.30

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Supposed “[REDACTED]”

- 1.0mg once-weekly Ozempic®’s success is not due to supposed [REDACTED] as Dr. McDuff argues (although the Reply did not).

EX1308 (McDuff Decl.), ¶¶59-64; SurRep. 28 n.20

— [REDACTED]

EX2300 (Velturo Decl.), ¶110; POR.82; SurRep. 28 n.20

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Supposed “[REDACTED]” (cont'd)

- PO’s strategy presentations confirm that [REDACTED]

[REDACTED]

EX2300 (Vellturo Decl.), ¶1111; EX2323 (Ozempic® Launch Tracker), 7-9; POR.82; SurRep.28

- [REDACTED]

[REDACTED]

EX2300 (Vellturo Decl.), ¶1111; EX2315 (Ozempic® Launch Tracker), 7-9; POR.82; SurRep.28

- And, by failing to discuss this [REDACTED]” argument in the Reply (it is suggested only in Dr. McDuff’s declaration), Petitioner **waived** it.

SurRep.28 n.20

- Even if considered, Dr. McDuff’s testimony on this point falls to pass muster.
- Dr. McDuff opined that [REDACTED] occurred, but he **ignored contrary evidence in documents on which he relied.**

EX2555 (McDuff Dep. Tr.), 53:11-54:21 (discussing EX2314 (Semaglutide Ad Board Market Overview)); SurRep.28 n.20

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Supposed “[REDACTED]” (cont'd)

Q. So you would agree that Novo Nordisk was looking for a favorable co-existence of both Victoza and semaglutide?

A. I can't speak to their strategy overall. This is the first time I'm seeing this language, "favorable co-existence." But certainly, I see it here in the document.

Q. You relied on this document in forming your opinions, correct?

A. Yes.

EX2555 (McDuff Dep. Tr.), 54:11-21; SurRep.28 n.20

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Pricing

- 1.0mg once-weekly Ozempic®'s success is not due to [REDACTED].
 - [REDACTED]
 - Petitioner **never challenged this conclusion**, failing to put forward any evidence or argument to the contrary.

EX2300 (Velturo Decl.), ¶¶113-16; EX2334 (Pre-POA Opening Presentation), 74-78; POR.82

SurRep.28 n.20

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Potential Blocking Patents

- There is no evidence that blocking patents detract from 1.0mg once-weekly Ozempic®'s commercial success.

EX2300 (Velturo Decl.), ¶¶117-120; POR.82-83

- A “blocking patent” is an earlier patent infringed by a later invention that “may deter non-owners and non-licensees from investing the resources needed to make, develop, and market such a later, ‘blocked’ invention, because of the risk of infringement liability and associated monetary or injunctive remedies.”

Acorda Therapeutics, Inc. v. Roxane Labs., Inc., 903 F.3d 1310, 1337 (Fed. Cir. 2018); POR.83

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Blocking Patents (*cont'd*)

- Dr. Vellturo considered two of PO's patents that cover the compound semaglutide—'343 and '122—and could potentially have been blocking patents, but based on his analysis he concluded they would not have significantly diminished the incentives for third-party development of '462.

EX2300 (Vellturo Decl.), ¶¶117-120; POR.82-83; SurRep.31-32

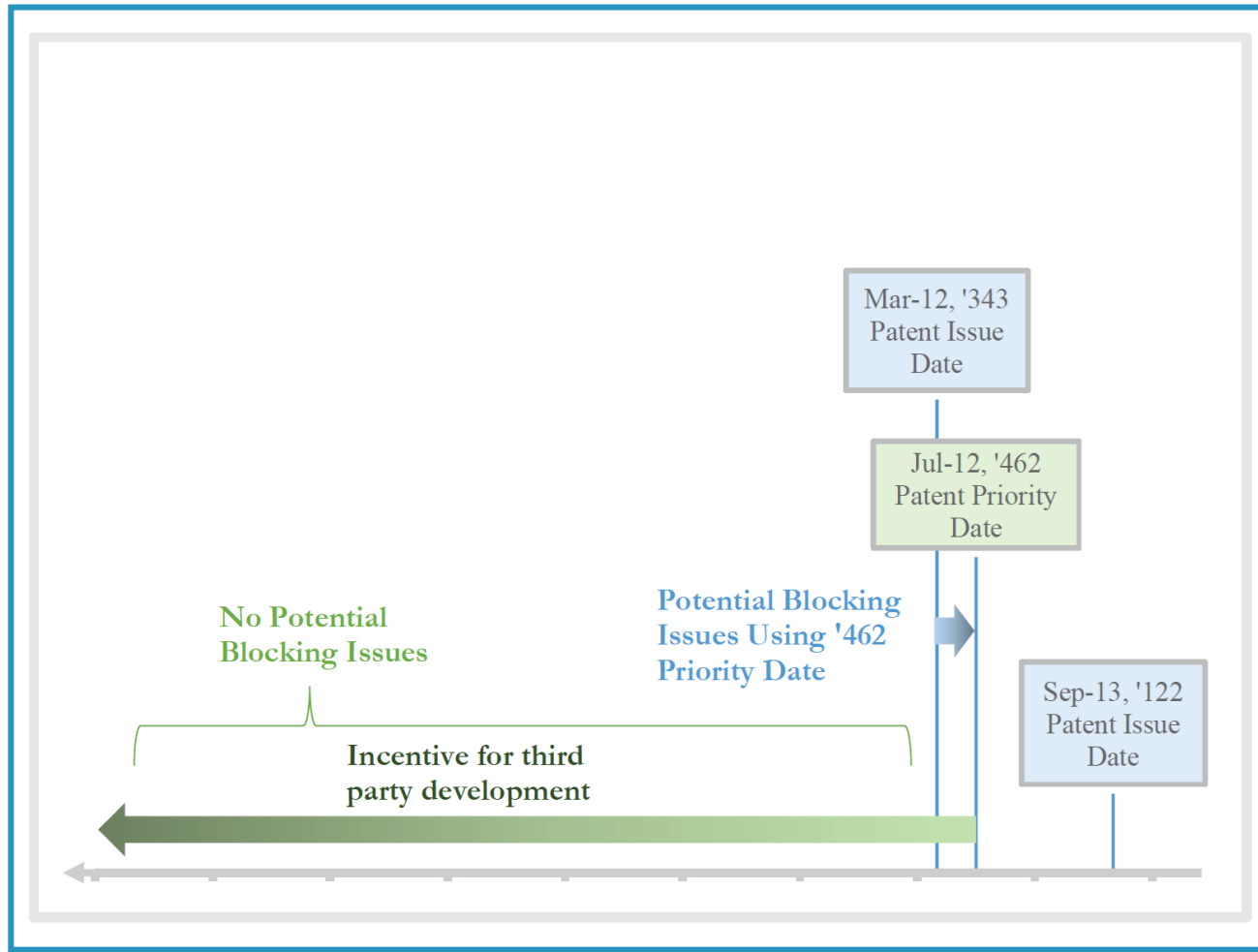
- '122 issued **after** '462's latest priority date (July 1, 2012) and thus cannot be a blocking patent.

EX2488 ('122 Patent), 1; POR.83

- '343 issued approximately **four months** before '462's latest priority date (July 1, 2012) and thus had at most a minimal impact in disincentivizing the invention of '462.

EX2487 ('343 Patent), 1; POR.83

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Blocking Patents (*cont'd*)



EX2300 (Vellturo Decl.), ¶120, Fig. 5 (Timeline of Potential Blocking Patent Considerations); POR.83

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Blocking Patents (*cont'd*)

- Petitioner contends the existence of the ***application*** leading to '343 was sufficient to be blocking, but cites no law in support.

Rep.38-39; SurRep.31

- However, the law refers to blocking ***patents*** (not blocking *applications*) because it is the “claims of a **patent** [that] define the invention”—not pending application claims that **may never issue**.

Phillips v. AWH Corp., 415 F.3d 1303, 1312 (Fed. Cir. 2005) (en banc); SurRep.31

A blocking **patent** is **one that *is in place*** before the claimed invention...

Chemours Co. FC, LLC v. Daikin Indus., Ltd., 4 F.4th 1370, 1379 (Fed. Cir. 2021); SurRep.31

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Blocking Patents (*cont'd*)

- Dr. McDuff agrees that not every published patent application results in an issued U.S. patent.

EX2555 (McDuff Dep. Tr.), 63:21-64:1; SurRep.31

- But Dr. McDuff testified it was “**not necessary**” for his opinions for him to consider whether, at the time of publication of the application that led to the '343, it was likely that ***the claims as published then*** would actually issue.

EX2555 (McDuff Dep. Tr.), 66:1-12; SurRep.31

- But as *Acorda* indicates, in discussing a related **likelihood of claim viability**, “whether the blocking patent can be successfully challenged” is a “relevant” factor to be considered.

903 F.3d at 1338; SurRep.31

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: Blocking Patents (*cont'd*)

- Petitioner further contends that another of PO's patents (No. 8,114,833) that "cover[s] certain formulations of GLP-1 compounds" and issued in 2012 is a blocking patent.

Rep.39

- But this ignores Petitioner's admission that **other companies** were developing GLP-1 compound formulations ***after*** the 2012 issuance of the '833 patent.

EX2555 (McDuff Dep. Tr.), 62:4-2; SurRep.32

- Indeed, the record confirms **several other GLP-1 drugs were approved *after* 2012.**

EX2445 (Dulaglutide); EX2455 (Adlyxin); EX2475 (Mounjaro); SurRep.32

1.0mg Once-Weekly Ozempic® Has Been an Astounding Commercial Success: FDA Exclusivity

- Later-granted FDA exclusivity cannot detract from commercial success.
 - Petitioner’s expert, Dr. McDuff—but not Petitioner’s Reply—agrees FDA exclusivity detracted from ‘462’s commercial success.

EX1308 (McDuff Decl.), ¶¶86-88; SurRep.32

- But even if considered, this exclusivity was not granted before ‘462’s issuance, but, instead, **five years after** ‘462 issued.

SurRep.32

- And **Dr. McDuff’s testimony** that “the **expectation** that a five-year chemical entity **exclusivity period will exist at some point**[,] [i]t’s that length of time that acts as an economic deterrent” **must be rejected as nonsensical**: it would mean that **no new chemical entity** could ever be commercially successful.

EX2555 (McDuff Dep. Tr.), 68:6-12, 69:22-70:10; SurRep.32

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D

- An “improved efficacy and a better safety profile” have been found to demonstrate unexpected results.

Allgenesis Biotherapeutics, Inc. v. Cloudbreak Therapeutics, LLC, IPR2020-01438, Pap.29, 77 (Feb. 15, 2022); POR.83-84

- While **post-invention data** may prove **unexpected results**, the question of **what POSITA would have found surprising or unexpected** 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); SurRep.33

While we have permitted evidence from after the patent is granted to be considered in assessing whether there are unexpected results, the results must be unexpected by one of ordinary skill in the art at the time of the application.

Forest Lab’ys, 918 F.3d at 937 (internal quotation marks and citations omitted); SurRep.33

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: HbA_{1c} and Weight Loss

- The **significant reduction in HbA_{1c} and weight loss in T2D patients using Ozempic® is unexpected** in comparison to previously-available medications for treating T2D, including the closest prior art—other GLP-1 analogues (or, as Petitioner appears to suggest, semaglutide *but with no data*).

EX2054 (Goland Decl.), ¶¶57-76; POR.83

 - **Once-weekly** 1.0mg Ozempic® provides **superior HbA_{1c} control and weight loss** as compared to **once-daily liraglutide** at **1.2 or 1.8mg**.

EX1001 ('462 Patent), Figs. 1 and 5; EX2054 (Goland Decl.), ¶¶61-63, 65, 76; POR.84
 - 1.0mg once-weekly Ozempic® was also **superior for HbA_{1c} control and weight loss** as compared to **higher doses of other once-weekly GLP-1 analogues** such as **dulaglutide (0.75 and 1.5 mg) and exenatide ER (2.0mg)**.

EX2054 (Goland Decl.), ¶¶65-73; POR.84
- As Dr. Goland testified, **POSITA would not have expected these superior outcomes** using '462's claimed methods.

EX2054 (Goland Decl.), ¶¶65-73; POR.84

 - Instead, patients prescribed Ozempic experienced **significant HbA_{1c} reductions** POSITA would not have expected from a once-weekly treatment.

EX2054 (Goland Decl.), ¶177; POR.84
 - And, **POSITA would have expected that such weight loss would be possible only with bariatric surgery.** This was especially true given that **most other T2D treatments caused weight gain.**

EX2054 (Goland Decl.), ¶¶50-59, 64-65, 87, 40-49; POR.84

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular

- 1.0mg once-weekly subcutaneous semaglutide also demonstrated **unexpected superiority** as compared to placebo for **cardiovascular endpoints** in a clinical trial designed simply to show **cardiovascular safety**.

EX2055 (Blaha Decl.), ¶¶34-36; POR.86

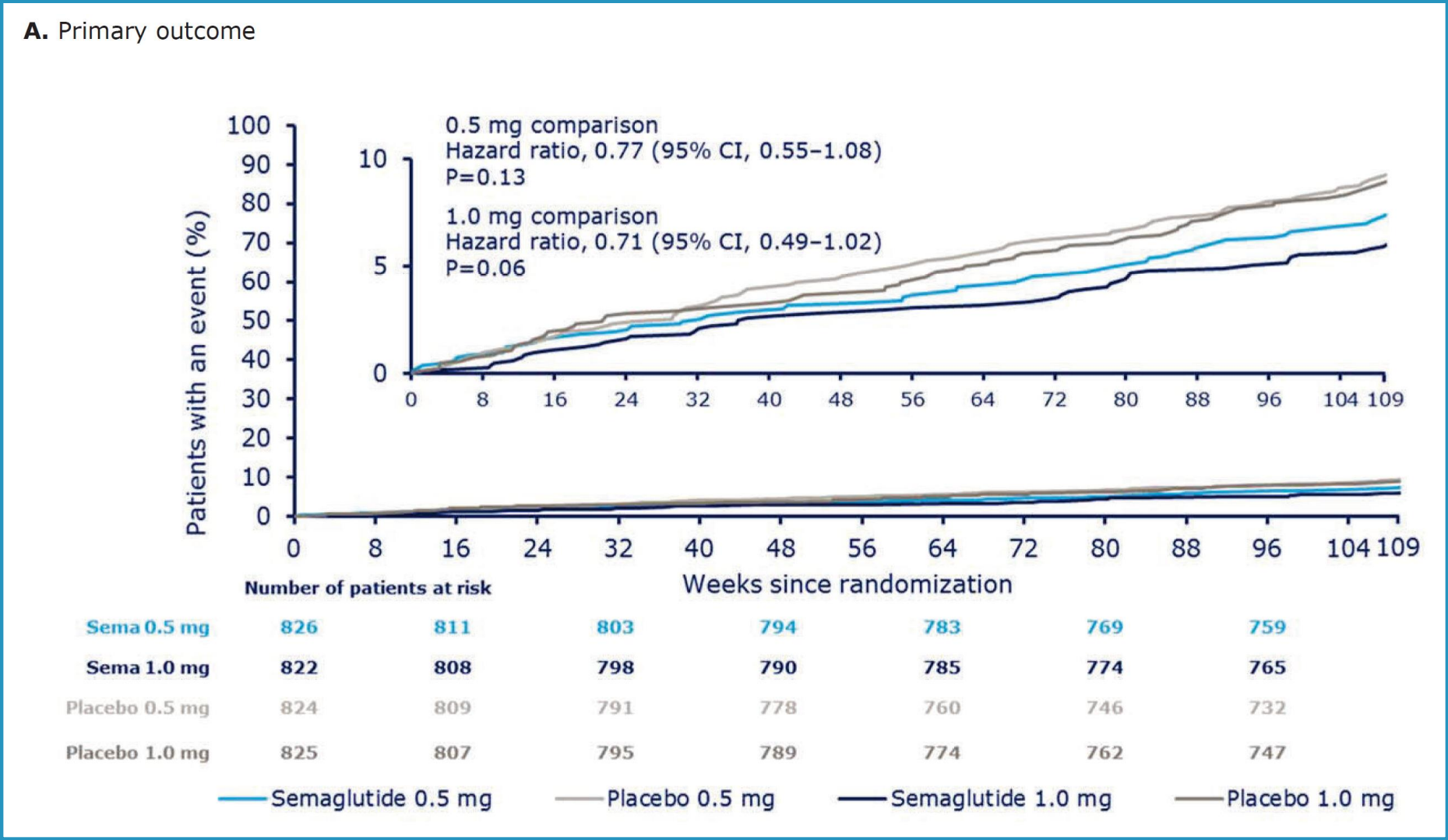
- Across both tested semaglutide doses (0.5mg and 1.0mg), there was a 26% reduction in major adverse cardiovascular events (MACE), including a statistically significant 39% decrease in nonfatal stroke.

EX2055 (Blaha Decl.), ¶¶34-36; EX2101 (Marso), 8-10; POR.86

- **1.0mg once-weekly semaglutide**, in particular, had a **MACE reduction of 29%.**

EX2055 (Blaha Decl.), ¶37; EX2102 (Marso Supplementary Appendix), 44; POR.86

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular (cont'd)



EX2102 (Marso Supplementary Appendix), 44; EX2055 (Blaha Decl.), ¶37; POR.86

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular (*cont'd*)

- The clinical data trended towards **greater benefit** for **1.0mg once-weekly subcutaneous semaglutide** in the **components of MACE**, specifically a **38% reduction in myocardial infarction for 1.0mg** vs. 12% reduction for 0.5mg semaglutide.

EX2055 (Blaha Decl.), ¶37; EX2102 (Marso Supplementary Appendix), 45-47; POR.87

- **1.0mg once-weekly subcutaneous semaglutide** also showed **more benefit on other intermediate cardiovascular outcomes** that are **highly important in everyday clinical practice**, such as **systolic blood pressure, HDL/cholesterol ratio, and triglycerides**.

EX2055 (Blaha Decl.), ¶37; EX2102 (Marso Supplementary Appendix), 50, 102-105; POR.87

- Cardiovascular outcomes benefits seen with 1.0mg once-weekly semaglutide (1) are **unlikely to be explained solely by reduction in HbA_{1c}, blood pressure, or weight, and** (2) were **seen across essentially all subgroups of patients**—regardless of baseline BMI, gender, age, or cardiovascular risk.

EX2055 (Blaha Decl.), ¶¶40, 42; EX2110 (Verges), 3-6; EX2111 (Verma), 3; EX2100 (Leiter), 3, 9-10; POR.87

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular (*cont'd*)

- 1.0mg once-weekly semaglutide's 29% MACE reduction was particularly notable compared with the closest prior art, 1.8mg daily liraglutide, which had an already-impressive 13% reduction in MACE.

EX2055 (Blaha Decl.), ¶¶37-38; EX2102 (Marso Supplementary Appendix), 44; POR.86

- Petitioner complains this comparison is not against the closest prior art, because (Petitioner misleadingly suggests) semaglutide was known to exist in the prior art for more than a decade.

Rep.41

- But as Petitioner's Dr. Schwartzbard confirmed, there was **no data on cardiovascular outcomes for Ozempic® prior to 2016**—4 years *after* the latest possible priority date for '462.

EX2557 (Schwartzbard Dep. Tr.), 22:13-17, 25:22-26:4, 26:17-27:4; SurRep.32-33

- And, as Dr. Schwartzbard acknowledged, comparisons against the **“closest prior art”** must be **“what was available to physicians** prior to the patent that we're discussing.”

EX2557 (Schwartzbard Dep. Tr.), 20:3-8; SurRep.32-33

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular (*cont'd*)

- The **reduction in nonfatal stroke** appears to be **more robust (and clinically relevant)** for **semaglutide** across both tested doses **as compared to 1.8mg liraglutide**.

EX2055 (Blaha Decl.), ¶¶38, 41; EX2110 (Verges), 2; POR.86

- The unexpected results for 1.0mg once-weekly semaglutide were **also surprising and unexpected in view of** previously-completed research with **DPP-4 inhibitors**, which had shown ***no* MACE-reduction benefit**.

EX2055 (Blaha Decl.), ¶43; EX2105 (Nauck), 2, 11; POR.86

- While Petitioner criticizes this comparison, Petitioner's cardiovascular expert, **Dr. Schwartzbard, published articles making this exact type of comparison of GLP-1s to DPP-4 inhibitors**.

Rep.39; EX1246 (Smilowitz & Schwartzbard), 1-2; SurRep.33

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Cardiovascular (*cont'd*)

- Petitioner's **Dr. Schwartzbard** *now* argues these results were ***not unexpected*** because there was **no expectation** that **GLP-1s** generally would cause cardiovascular ***harm***.

See, e.g., EX1304 (Schwartzbard Decl.), ¶1113; SurRep.36-37

- But **Dr. Schwartzbard's own articles** *predating* this litigation **contradict this opinion**, undermining any credibility of his current testimony.

SurRep.37

- In **2014**, Dr. Schwartzbard wrote there were **"conflicting findings"** and a **"dearth of data"** regarding GLP-1 agonists and heart failure; that **"clinical trials [were] necessary to establish safety"**; and that **"[n]ew pharmacological agents are urgently needed."**

EX1246 (Smilowitz & Schwartzbard), 4, 6-7; SurRep.36-37

- In **2018**, Dr. Schwartzbard wrote that then-upcoming trials would **"help clarify whether the CV [cardiovascular] 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 (Schwartzbard Dep. Tr.), 51:19-52:12, 56:6-57:9; SurRep.36-37

- And in **2020**, Dr. Schwartzbard acknowledged **"HF [heart failure] was an initial concern with GLP1RA use."**

EX2601 (Wilcox & Schwartzbard), 13; see also EX2557 (Schwartzbard Dep. Tr.), 39:7-12, 40:21-41:14; SurRep.36-37

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits

- **No data regarding kidney protection** existed for **semaglutide 1.0mg** once weekly administered subcutaneously until **well *after* any priority date** for '462.

EX2011 (Bakris Decl.), ¶¶44-46, 57; POR.84-85

- In clinical trial data that compared **1.0mg once-weekly semaglutide** with **0.5mg once-weekly semaglutide** and **1.8mg daily liraglutide** in T2D patients, “the largest magnitude of [kidney] protective effects [was] observed for **semaglutide 1.0mg.**”

EX2015 (Shaman), 8, 2, 5, 9; EX2011 (Bakris Decl.), ¶¶47-51; POR.85

- **Further trials** showed **surprising results with reductions in several markers of chronic kidney disease** with **1.0mg once-weekly semaglutide.**

EX2011 (Bakris Decl.), ¶¶52-56; EX2013 (Heerspink), 1, 4-5, 9; EX2012 (Rossing), 9-10; POR.85

- There is ***additional* benefit** from **1.0mg once-weekly semaglutide** that “does not appear to be explained or accounted for by changes in [reduction in HbA_{1c}, body weight, and blood pressure] alone.”

EX2013 (Heerspink), 9; EX2011 (Bakris Declaration), ¶¶55-56; POR.85

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- PO actually **stopped a Phase IIIb trial** evaluating the effects of semaglutide on kidney outcomes **due to the superior efficacy of 1.0mg once-weekly semaglutide** as compared to placebo.

EX2011 (Bakris Decl.), ¶¶58-62; POR.85

- For example, 1.0mg once-weekly semaglutide significantly reduced the risk of major kidney disease events by 24% and the risk of death from any cause by 20% as compared to placebo.

EX2604 (Perkovic), 1, 11; SurRep.36

- The trial was stopped because **patients receiving 1.0mg once-weekly semaglutide had such unexpected improvements that it would have been unethical to continue administering placebo** to patients in the placebo arm.

EX2011 (Bakris Decl.), ¶¶62-63; POR.85-86

- Such a stoppage is “**very rare.**”

EX2011 (Bakris Decl.), ¶¶62-63; POR.86

- Even **Petitioner’s expert admitted** this “FLOW” study was “**groundbreaking.**”

EX2554 (Coca Dep. Tr.), 10:17-12:22; SurRep.36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Petitioner's kidney expert, Dr. Coca, **by his own admission *misquoted, mischaracterized,* and *overstated*** the articles on which he relied, rendering his opinions unreliable.

SurRep.34-35

- For example, Dr. Coca purported to quote EX1149 as support in his declaration, but **the “quote” he presented to the Board *doesn't exist*.**

EX1306 (Coca Decl.), ¶179 (citing EX1149 (Gutzwiller), 6); EX2554 (Coca Dep. Tr.), 62:18-65:2; SurRep.34-35

79. By 2004, it was “documented that GLP-1 infusion dose-dependently increased sodium excretion and had a natriuretic effect in obese, insulin-resistant patients who suffered from type 2 diabetes.” EX1149 (Gutzwiller 2004) at 6.

EX1306 (Coca Decl.), ¶179 (citing EX1149 (Gutzwiller), 6);
EX2554 (Coca Dep. Tr.), 62:18-65:2; SurRep.34-35

Discussion

This study demonstrates that the infusion of synthetic human GLP-1 significantly increased natriuresis in healthy male subjects and in obese, insulin-resistant men. The effects of GLP-1 on the kidney broaden the spectrum of the biological actions of the peptide, in addition to its well-known effects on blood glucose and insulin release. We have previously reported that food and water intake were diminished with continuous GLP-1 infusion in patients suffering from type 2 diabetes mellitus (16). Here we have **documented that GLP-1 infusion dose-dependently increases urinary sodium excretion in healthy male volunteers.** The natriuretic effect of GLP-1 was confirmed in obese, insulin-resistant patients,

EX1149 (Gutzwiller), 6; EX2554 (Coca Dep. Tr.), 66:9-72:13; SurRep.35

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca purported to quote EX1149 as support in his declaration, but the “quote” he presented to the Board ***doesn’t exist***.

EX1306 (Coca Decl.), ¶79 (citing EX1149 (Gutzwiller), 6); EX2554 (Coca Dep. Tr.), 62:18-65:2; SurRep.34-35

Q. So, do you see in paragraph 79 you wrote, “It was documented that GLP-1 infusion dose independently increased sodium secretion and had a natriuretic effect in obese, insulin-resistant patients who suffered from type 2 diabetes.” Do you see that?

A. **I see that.**

Q. And you cite Exhibit 1149 as support?

A. **Yes.**

* * *

Q. Correct. For the record, Dr. Coca, **this is what you have put as a quote from Exhibit 1149.**

A. **Correct.**

Q. **Do you agree, do you think that is a fair characterization of Exhibit 1149?**

A. **I do. But I’d be happy to review the data jointly.**

EX2554 (Coca Dep. Tr.), 62:18-65:2, 66:9-72:13; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca purported to quote EX1149 as support in his declaration, but the “quote” he presented to the Board ***doesn’t exist***.

EX1306 (Coca Decl.), ¶79 (citing EX1149 (Gutzwiller), 6); EX2554 (Coca Dep. Tr.), 62:18-65:2; SurRep.34-35

Q. Could you show me where on page 6, or anywhere else, this quote is found?

A. **I cannot find this exact quote. The first sentence under discussion is very similar, but – instead of --.**

* * *

A. **Well -- well, Josh, what I see is that I can’t find the exact quote, but I would say the spirit of the line and then, perhaps, I shouldn’t have used exact quotation, is supported by the data. And I can point to here the factual excretion of sodium in Table 2, with the lower dose versus the higher dose of GLP-1, the secretion increased from 1.7 to 2.7 percent.**

* * *

Q. Yep. Please proceed, Dr. Coca.

A. **Well, what I’m also realizing, in clarification, is that Table 2 is reflective of healthy subjects and not the obese, insulin-resistant subjects.**

EX2554 (Coca Dep. Tr.), 62:18-65:2, 66:9-72:13; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca purported to quote EX1149 as support in his declaration, but the “quote” he presented to the Board ***doesn’t exist***.

EX1306 (Coca Decl.), ¶79 (citing EX1149 (Gutzwiller), 6); EX2554 (Coca Dep. Tr.), 62:18-65:2; SurRep.34-35

Q. You had – in paragraph 79 and you had cited to Exhibit 1149, page 6. Do you see that?

A. **I see that.**

Q. And does that quote appear after you’ve reviewed Exhibit 1149, **does that quote appear anywhere** in Exhibit 1149, yes or no?

A. **No, I do not see it.**

Q. And if we go to page 6, and I’ll note, for the record, that you’re able to scroll. If we go to page 6, at the discussion, I think **what it appears you actually were trying to quote** is the sentence that states “Here, we have documented that GLP-1 dose-dependently increases urinary sodium excretion **in healthy male volunteers.**” Do you see that sentence?

A. **Yes, I do.**

EX2554 (Coca Dep. Tr.), 66:9-72:13, 62:18-65:2; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca repeatedly overstated the conclusions of his articles to argue kidney-protective effects were **certain** or **expected**.

SurRep.35-36

- But, instead, his articles described:

- **Early hypotheses based on soft endpoints in rodent studies.**

EX2554 (Coca Dep. Tr.), 13:12-18 (blood glucose and blood pressure, both of which are soft endpoints); 42:10-43:1 (animal studies, which are insufficient on their own); SurRep.35-36

- Studies in **small groups of healthy** volunteers where the authors were “**speculat[ing]**” or needed their “**hypothesis needs** to be confirmed by other studies,” also based on **soft endpoints**.

EX2554 (Coca Dep. Tr.), 13:12-18, 55:5-16, 59:4-62:17, 72:20-74:10, 79:5-22; SurRep.35-36

- **Safety studies investigating concerns about using GLP-1 receptor agonists in patients with kidney issues.**

EX2554 (Coca Dep. Tr.), 85:12-97:7, 146:17-147:11; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

Q. And in paragraph 80 you write that the prior art study being discussed described GLP-1 as being able to “reverse this vicious cycle” and represented a new treatment regimen for patients with type 2 diabetes. Do you see that?

A. **I see that.**

Q. And this is also referring to Exhibit 1149?

A. **I believe so.**

Q. So while you describe these prior art studies as describing GLP-1 as being able to reverse this vicious cycle, we go ahead down to the last paragraph on page 7. Do you see the actual citation is -- or actual quote is “we speculate that GLP-1 could reverse this vicious cycle?” Do you see that?

A. **I see that.**

Q. Do you think you overstated the conclusion that Exhibit 1149 drew at all?

A. **Perhaps including the word “could” would be prudent.**

Q. And maybe that they were speculating? Would that have also been prudent to include?

A. **I guess the word “could” adds a notion of speculation.**

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca presented two articles describing the data from **one study** as **two separate studies**.

SurRep.36

- **Vollenweider (EX1147)** discusses a study by **Yu (EX1148)**.
- But Dr. Coca describes **Vollenweider** as discussing “**Other studies**” **in addition to Yu**.

EX1306 (Coca Decl.), ¶¶77-78; EX2554 (Coca Dep. Tr.), 50:7-58:13; SurRep.35-36

77. It was also well established in the art by 2010 that GLP-1 agonists demonstrated *at a minimum* kidney protective effects, and were in fact likely to directly treat CKD and DKD. Indeed, well before the priority date of the '462 patent, it was known GLP-1 receptors are expressed in the kidney. EX1148 (Yu) at 2. And studies in Dahl-sensitive rats that were also insulin-resistant and hyperlipidemic concluded that the administration of GLP-1 “significantly attenuated the development of protein and albuminuria and prevented the rise in plasma creatine concentration.” *Id.* at 6. Thus, by 2003, it was already known that GLP-1 would at least reduce renal organ damage, if not directly benefit the kidneys. *Id.* at 4, 7, 10.

78. Other studies also demonstrated “that GLP-1 had a diuretic and strong natriuretic action, resulting in a negative cumulative sodium balance.” EX1147 at 1.

EX1306 (Coca Decl.), ¶¶77-78; SurRep.35-36

Q. Yep. So Exhibit 1147 is discussing native GLP-1 in Dahl S rats; is that correct?

A. Yes, actually this is -- **it's a perspective piece, largely written in conjunction with the Yu paper, so it's kind of taking the finding by Yu, in Exhibit 1148, and putting them into bigger context.**

* * *

Q. No. **In paragraph 78, when you said “other studies,” you were only referring to Yu; is that correct?** By Yu, I mean 11 – Exhibit 1148?

A. **Yeah, it is circling back to the Yu study, which paragraph 77, so -- .**

EX2554 (Coca Dep. Tr.), 51:16-22, 55:17-56:18; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca also repeatedly overstated conclusions relating to ***rodent studies*** or ***safety studies*** in humans to argue kidney-protective effects were **certain** or **expected** in humans, but he agreed at deposition that the **articles on which he relied did not draw those conclusions.**

EX2554 (Coca Dep. Tr.), 62:3-17, 85:12-97:7; SurRep.35-36

Q. And in Exhibit 1147, their actual conclusion was that with such new tools, referring to the longer-acting analogs, it would be possible to test whether the antihypertensive actions of GLP-1, **seen in Dahl salt-sensitive rats**, are also encountered in human disease states. Do you see that?

A. **I see that.**

Q. **So these authors didn't conclude that these will be expected in human disease states, fair?**

A. **Fair. And I give them credit for not overstating what these results mean.**

EX2554 (Coca Reply Dep. Tr.), 62:3-17; SurRep.35-36

Q. Do you agree that Exhibit 1156, the Jacobsen study, was a safety study?

A. **Well, this is a PK study of liraglutide, and, typically, PK studies are more about safety than efficacy.**

Q. **And their conclusion was, as you phrased it, liraglutide could be safely administered to CKD patients at the approved doses.** Do you see that?

A. **I see that.**

EX2554 (Coca Reply Dep. Tr.), 85:18-86:7; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca also repeatedly overstated conclusions relating to ***rodent studies*** or ***safety studies*** in humans to argue kidney-protective effects were **certain** or **expected** in humans, but he agreed at deposition that the **articles on which he relied did not draw those conclusions.**

EX2554 (Coca Dep. Tr.), 62:3-17, 85:12-97:7; SurRep.35-36

Q. So for Exhibit 1157, you see it has a copyright date of 2011?

A. **Yes, I see that.**

Q. And if you go to the abstract on the first page, please. Do you see that in the objective, it says to “determine the effect of mild renal impairment on the efficacy and safety of liraglutide in patients with type 2 diabetes”?

A. **I see that.**

* * *

Q. You’d agree with me that their conclusion was that liraglutide was safe in patients with type 2 diabetes and mild renal impairment, correct?

A. **Correct.**

Q. And they expressly note that “Further studies and more experience in patients with T2DM and more advanced degrees of renal failure will ultimately be required to better characterize the efficacy and safety profile in this patient population.” Do you agree with that?

A. **That’s what they state, yes.**

EX2554 (Coca Reply Dep. Tr.), 91:17-94:15; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca also repeatedly **ignored contrary evidence** in his own cited articles.

EX2554 (Coca Dep. Tr.), 50:7-58:13, 77:11-79:22; SurRep.36

Q. And if we turn to Exhibit 1147 at page 2, and it says, at the top of the first paragraph, “The results contrast with previously published data showing that GLP-1 or LGP-1 receptor agonist administration **acutely increased blood pressure and heart rate** in rats. Do you see that?

A. **I see that.**

Q. **Okay. Did you address this discrepancy at all in your declaration?**

A. **No, I did not.**

EX2554 (Coca Reply Dep. Tr.), 56:19-57:7; SurRep.35-36

1.0mg Once-Weekly Ozempic® Has Demonstrated Unexpected Benefits in the Treatment of T2D: Kidney-Protective Benefits (*cont'd*)

- Dr. Coca also repeatedly **ignored contrary evidence** in his own cited articles.

EX2554 (Coca Dep. Tr.), 62:3-62:17, 77:11-79:22; SurRep.36

81. Further, in 2006, Gutzwiller characterized GLP-1's renal effects and looked specifically at the mechanism by which GLP-1 was inducing a reduction in intestinal sodium absorption. EX1163 (Gutzwiller 2006) at 1, 8. Gutzwiller 2006 found that "GLP-1 increases sodium excretion by the kidneys to control extracellular volume expansion, and may reduce sodium absorption by the gastrointestinal tract to prevent volume expansion." *Id.* at 8. Thus, this evidence further demonstrated that GLP-1 "seem[ed] to play a significant role in sodium and water homeostasis," which are critical to healthy kidney function. *Id.*

EX1306 (Coca Decl.), ¶181; SurRep.35-36

Q. Do you see you cite Exhibit 1163 for support of your assertion that Gutzwiller characterized GLP-1's renal effects and looked specifically at the mechanism by which GLP-1 was inducing a reduction in internal -- intestinal sodium absorption? Do you see that?

A. **Yes.**

Q. **Do you mention, in paragraph 81, in discussing Exhibit 1163, that the study was in healthy male subjects?**

A. **No.**

EX2554 (Coca Dep. Tr.), 77:11-79:22; SurRep.35-36

The Proper Comparison for Unexpected Results Is Against the Closest Prior Art *with Data*

- Petitioner complains that PO's evidence of unexpected results was not compared against 0.8mg once-weekly semaglutide, which Petitioner contends was known in the prior art, or 1.8mg once daily liraglutide.

Rep.39

- But Petitioner's experts all agreed that there was **no data at the priority date for 0.8mg once-weekly semaglutide**, and **often no relevant data for 1.8mg liraglutide**.

EX2554 (Coca Dep. Tr.), 105:7-106:19 ("Q. Okay. So to be clear, **as of 2012, there was no known data for any dose of semaglutide, correct? A. Not that I'm aware of.**");

EX2557 (Schwartzbard Dep. Tr.), 22:13-17, 26:17-27:4, 20:3-8; SurRep.25, 32-33

- Moreover, PO ***did* compare against 1.8mg liraglutide when such data was available**.

EX2015 (Shaman), 8; POR.33, 84-85, 88; SurRep.32 n.21; EX2556 (Spiegel Dep. Tr.), 129:10-132:1

- 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's, LLC v. Sigmapharm Lab's, LLC*, 918 F.3d 928, 937 (Fed. Cir. 2019); SurRep.33

Petitioner Improperly Assumes That All Differences in Percentages Are Merely Differences in Degree

- “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); SurRep.34

- The question of where to “draw [the] line between difference in degree . . . and difference in kind” is a “fact-specific” inquiry.

Amgen Inc. v. Sandoz Inc., 66 F.4th 952, 964 (Fed. Cir. 2023); SurRep.34

- Here, the unexpected results evidence PO presented shows differences in **kind** and not just differences in **degree**.

EX2054 (Goland Decl.), ¶¶61-83; EX2055 (Blaha Decl.), ¶¶34-33; EX2011 (Bakris Decl.), ¶¶44-63; EX1001 ('462 Patent), Fig. 5; EX2082 (SUSTAIN 10), 1, 6-7; POR.83-87; SurRep.34

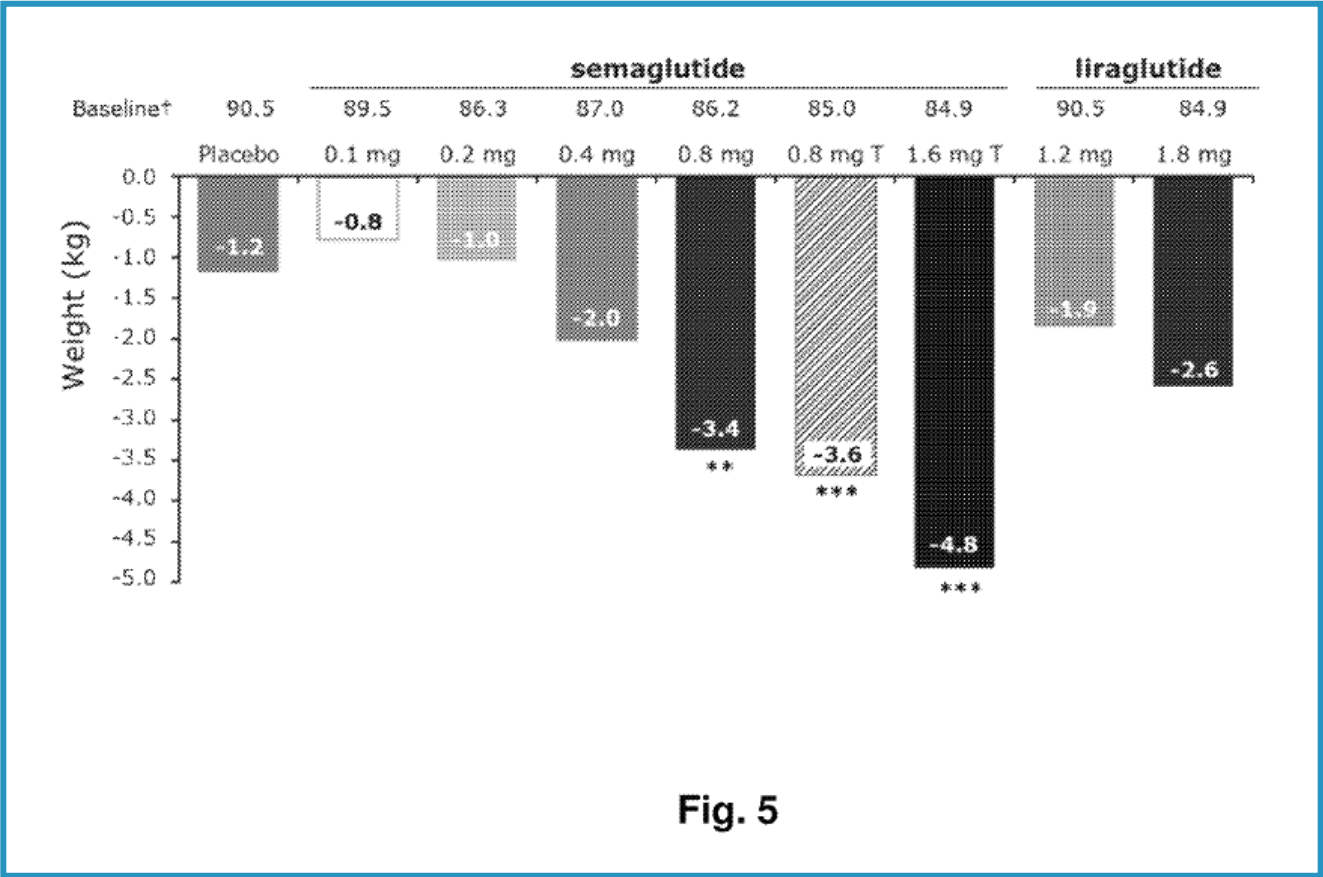
- But Petitioner’s experts consistently failed to understand this legal principle.

EX2557 (Schwartzbard Dep. Tr.), 27:18-29:7; EX2554 (Coca Dep. Tr.), 118:6-119:4; EX2556 (Spiegel Dep. Tr.), 41:22-44:2; SurRep.34

The Differences Here Are Differences in Kind

- For example, the '462 Patent demonstrated there is a 30.8% greater weight loss with 0.8mg semaglutide (3.4kg) than 1.8mg liraglutide (2.6kg)

EX1001 ('462 Patent), Fig.5; SurRep.34



The Differences Here Are Differences in Kind

- And the SUSTAIN 10 trial compared 1.0mg semaglutide against 1.2mg liraglutide over 30 weeks, again confirming a difference in kind:

EX2082 (SUSTAIN 10), 1, 6-7; SurRep.34

- **211% more patients hit 5% weight loss** (56% with semaglutide v. 18% for liraglutide).

EX2082 (SUSTAIN 10), 1, 6-7; SurRep.34

- **375% more patients hit 10% weight loss** (19% with semaglutide v. 4% for liraglutide).

EX2082 (SUSTAIN 10), 1, 6-7; SurRep.34

- **205% greater average weight loss** (5.8kg with semaglutide v. 1.9kg for liraglutide).

EX2082 (SUSTAIN 10), 1, 6-7; SurRep.34

- **70% greater reduction in HbA_{1c}** (1.7% reduction with semaglutide v. 1.0% for liraglutide).

EX2082 (SUSTAIN 10), 1, 6-7; SurRep.34

1.0mg Once-Weekly Ozempic® Satisfied a Long-Felt Unmet Need for a Safe, Effective, and Tolerable Once-Weekly T2D Treatment with HbA_{1c} and Weight Loss Benefits

- As Dr. Goland confirmed, a long-felt, unmet need existed for a **safe, effective, and tolerable** once-weekly method for treating T2D that significantly **reduced HbA_{1c}** and caused significant **weight loss**, which 1.0mg once-weekly Ozempic® satisfied.

EX2054 (Goland Decl.), ¶¶79-83, 40-58; POR.87-88

- And Petitioner’s **own experts testified as to** both the **existence** of this long-felt need and **how semaglutide** as used in ’462 **satisfied** it.

POR.87-88

- **Dr. Bantle:** “[S]emaglutide was an option that would be provided as a **once weekly injection, a significant improvement in the eyes of patients.**”

EX1003 (Bantle Decl.), ¶323; POR.87-88

- **Dr. Jusko:** Explaining—in describing “[f]urther research into the use of GLP-1 and its derivatives”—certain “**benefit[s] of once weekly dosing for GLP-1 receptor agonists in development**” such as **(1) improved compliance; (2) improved glycemic control; and (3) reduction in nausea.**

EX1005 (Jusko Decl.), ¶¶80-81; POR.87-88

1.0mg Once-Weekly Ozempic® Satisfied a Long-Felt Unmet Need for a Safe, Effective, and Tolerable Once-Weekly T2D Treatment with HbA_{1c} and Weight Loss Benefits (*cont'd*)

- Existing treatments that were effective at lowering HbA_{1c} actually **caused weight gain**.

EX2054 (Goland Decl.), ¶80; POR.88

- Existing GLP-1 analogues did **not cause weight loss** that **meaningfully impacted T2D**, and they **also had compliance issues**.

EX2054 (Goland Decl.), ¶¶81-82; POR.88

- Ozempic® satisfied this long-felt need.

EX2018 (Bantle Dep. Tr.), 20:2-21:14; EX2010, (Rosenstock Decl.) ¶¶178-91; POR.88

- Petitioner's expert criticizes this evidence because PO's expert, Dr. Goland, **relied on her own actual clinical experience** in reaching her conclusions.

See EX1303 (Spiegel Decl.), ¶212; SurRep.37

- But this only emphasizes **Dr. Spiegel's own lack of clinical treatment experience**: Spiegel has not “had direct responsibility for treating [] patient[s]” since **1976**.

EX2556 (Spiegel Dep. Tr.), 30:8-11, 37:20-39:17; SurRep.37

1.0mg Once-Weekly Ozempic® Has Been Extensively Praised

- Ozempic® has been **widely praised** by **patients, clinicians, prominent medical journals, and the media**—none of which Petitioner can deny.

EX2082 (SUSTAIN 10); EX2083 (SUSTAIN 4); EX2084 (SUSTAIN 7); EX2085 (SUSTAIN 3); EX2101 (Marso); EX2054 (Goland Decl.), ¶¶84-87, 62-74; EX2080 (The Year of Ozempic), 1; EX2081 (Whats Next For Ozempic), 2; POR.88-89; SurRep.38

Efficacy and safety of once-weekly semaglutide 1.0 mg vs once-daily liraglutide 1.2 mg as add-on to 1–3 oral antidiabetic drugs in subjects with type 2 diabetes (SUSTAIN 10)

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 randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial

Semaglutide versus dulaglutide once weekly in patients with type 2 diabetes (SUSTAIN 7): a randomised, open-label, phase 3b trial

Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes

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

What's Next
for Ozempic?

THE YEAR OF OZEMPIC

1.0mg Once-Weekly Ozempic® Has Been Extensively Praised (*cont'd*)

- Indeed, Petitioner's own expert admitted that patients praise Ozempic®.

EX2018 (Bantle Dep. Tr.), 125:4-19; POR.88

- Petitioner resorts to criticizing various articles as including PO's employees among their authors.

Rep.43

- But PO's involvement does not render **peer-reviewed and published data** of lesser value.

SurRep.38

- And Petitioner's own expert, Dr. Coca, admitted that articles **where PO's employees were involved** were “groundbreaking,” conducted by “respected scientist[s],” and “pertinent to [his] clinical practice and ... research.”

EX2554 (Coca Dep. Tr.), 10:17-12:22, 128:8-130:5; SurRep.38

1.0mg Once-Weekly Ozempic® Has Been Extensively Praised (*cont'd*)

- Ozempic® has also brought about a “**paradigm shift**’ in the **treatment and management of T2D**” in view of its **impressive and unexpected *cardiovascular* outcomes**, which has led to the creation of cardiometabolic clinics staffed with cardiologists who have the necessary expertise to treat both T2D and atherosclerotic cardiovascular disease.

EX2055 (Blaha Decl.), ¶¶45-46, 53; EX2088 (ACC Clinical Topics); EX2089; EX2093 (Cardiometabolic Fellowship); POR.89-90

- **Clinical practice guidelines** recommend using a small set of GLP-1 receptor agonists—semaglutide, liraglutide, and dulaglutide—in the treatment of T2D.

EX2055 (Blaha Decl.), ¶¶47-51; EX2090 (Consentino), 10, 26; EX2091 (Das ESC Guidelines), 11; EX2092 (Das ACC Guidelines), 11, 14, 16; EX2087 (ADA Standards of Medical Care), 14; POR.89

- The **American College of Cardiology specifically identifies** the “**potential for clinically relevant *heterogeneity*** within th[is] class” and **recommends using the 1.0mg dose** of once-weekly semaglutide **if the patient is treated with semaglutide**.

EX2055 (Blaha Decl.), ¶48; EX2092 (Das ACC Guidelines), 11, 14; POR.89

- Modeling suggests semaglutide may provide a **greater MACE reduction among T2D patients than dulaglutide**.

EX2055 (Blaha Decl.), ¶52; EX2095 (Evans), 1, 5-6; POR.89

1.0mg Once-Weekly Ozempic® Has Been Extensively Praised (*cont'd*)

- The writings of Petitioner’s own cardiovascular expert, Dr. Schwartzbard, contradict Petitioner’s attempt to refute the evidence of cardiovascular praise.

Rep.43; SurRep.38

- Dr. Schwartzbard wrote in **2018**—*before* being involved in this proceeding—that there had indeed been a “**paradigm shift**” based on what **may be a “drug-specific effect only seen with liraglutide and semaglutide”**:

EX2602 (Newman & Schwartzbard), 1, 10; EX2557 (Schwartzbard Dep. Tr.), 51:19-52:12; 52:16-53:11; 56:6-57:9; SurRep.38

1.0mg Once-Weekly Ozempic® Overcame Industry Skepticism

- As Dr. Goland confirmed:
 - In **2012** there were (and still are) **few once-weekly GLP-1 analogues available to treat T2D**, and **POSITA** would have been **skeptical others would be approved**.
EX2054 (Goland Decl.), ¶188; POR.90
 - **Following Ozempic®’s approval**, POSITA would have ***remained* skeptical that reported clinical trial results would actually be obtainable in *practice***.
EX2054 (Goland Decl.), ¶¶189-90; POR.90
 - But **Ozempic®** **overcame this skepticism** and **far *exceeded* the clinical trial results**.
EX2054 (Goland Decl.), ¶¶189-92; POR.90

Petitioner's Experts Should Be Given Little to No Weight

Dr. Bantle Applied an Incorrect REOS Standard

- Dr. Bantle asserted that a “**one-in-ten** chance of success [was] reasonable” “depend[ing] on the circumstances.”

EX2018 (Bantle Dep. Tr.), 92:6-93:5, 94:15-20; POR.56

- But the Federal Circuit has rejected REOS where there was “no more than a **fifty percent** chance of success.”

Amgen, Inc. v. Chugai Pharm. Co., 927 F.2d 1200, 1208 (Fed. Cir. 1991); POR.56

- Dr. Bantle also claimed that “one has to factor in the potential reward. So if the **potential reward** is likely to be **large**, then one is likely to **accept less of a reasonable expectation of success**.”

EX2018 (Bantle Dep. Tr.), 93:6-14, 93:21-94:7; POR.56

- But this is **contrary to the law: commercial success is evidence of non-obviousness**.

E.g., Alcon Rsch., Ltd. v. Apotex Inc., 687 F.3d 1362, 1366, 1371 (Fed. Cir. 2012) (“outstanding commercial success” of practicing product); POR.56

Petitioner's Experts' Incomplete, Unsupported, and Contradictory Opinions Should Be Given No Weight

- Petitioner's experts **lack a scientific and reasoned basis** for their opinions and provide **incomplete** analyses.

EX2552 (Bantle Reply Dep. Tr.), 22:8-16 (can't speak to Novo's intent); 28:11-29:3, 33:19-34:14, 36:16-20; EX2553 (Jusko Reply Dep. Tr.), 25:6-20, 35:16-36:9; SurRep.1-2 & n.2, 15 n.12, 17 n.13, 20 n.16, 25 & n.19, §III.D.2-3, 38-39; see also POR.29, 41 n.22, 49-50 & n.27, 54-57 & n.29, 58 n.34 (discussing Petitioner's experts' speculation about POSITA's knowledge of PO's non-public data);

- Dr. Bantle opines about semaglutide trials, but **never conducted a clinical trial evaluating any GLP-1 analog.**

EX2018 (Bantle Dep. Tr.), 15:10-17:3; *Mylan Pharms. Inc. v. AstraZeneca AB*, IPR2015-01340, Pap.79, 9-10 (Aug. 18, 2017); POR.41 n.22

- Dr. Bantle's opinions depend on how POSITA would have interpreted Phase I and II semaglutide trials, but Dr. Bantle conceded he is **not an expert in dosage selection for Phase I-III studies.**

EX2018 (Bantle Dep. Tr.), 112:15-113:1, 118:5-16; POR.54 n.29

- And Dr. Jusko similarly relies on how POSITA would have understood semaglutide protocols, but Dr. Jusko has **never prescribed any GLP-1 analogue or been involved in a clinical trial testing semaglutide or liraglutide.**

EX2019 (Jusko Dep. Tr.), 6:1--7:7; See *Mylan*, IPR2015-01340, Pap.79, 9-10; POR.54 n.29

Petitioner's Experts' Incomplete, Unsupported, and Contradictory Opinions Should Be Given No Weight

- Additionally, Dr. Bantle's and Dr. Jusko's written opinions **almost entirely duplicate one another, but they *repeatedly contradicted* each other at deposition**—despite Dr. Jusko having reviewed Dr. Bantle's deposition transcript and declaration in advance of Dr. Jusko's own deposition.

Compare, e.g., EX1300 (Bantle Reply Decl.), §§VI.D, VII.A-G with EX1301 (Jusko Reply Decl.), §§VII-VIII; see EX2552 (Bantle Reply Dep. Tr.), 9:7-12; Compare EX1003 (Bantle Decl.), §§ VII.A-E, IX with EX1005 (Jusko Decl.), §§ VIII.A-E, IX; Compare EX2552 (Bantle Reply Dep. Tr.), 15:20-16:20 (treatment even if it “makes a condition worse”) with EX2553 (Jusko Reply Dr. Tr.), 12:20-13:15, 14:7-15:4, 41:3-15 (treating requires tolerability and clinically meaningfully efficacy); POR.4 n.3; EX2019 (Jusko Dep. Tr.), 12:5-17, 59:21-60:14; SurRep.39

Petitioner’s Dr. Bantle Lacks Credibility and Contradicts Dr. Jusko

- For example, Dr. Bantle’s opinions that **something is a “treatment” even if it “makes a condition worse”** contradicts Petitioner’s Dr. Jusko, is incredible on its face, and should be ignored.
Compare EX2552 (Bantle Reply Dep. Tr.), 15:20-16:20 with EX2553 (Jusko Reply Dr. Tr.), 12:20-13:15, 14:7-15:4, 41:3-15; SurRep.39, 2 n.2

Dr. Bantle

Q.

Sure. Would claim 1 of the ‘462 patent be met, in your opinion, if the 1 milligram once-weekly semaglutide actually made diabetes worse in patients?

A.

Well, I’m not sure how to answer that question. I guess the key word there is ‘treating.’ And if a treatment makes a condition worse, is it still a treatment. I would say yes, it is; it’s just not a good treatment.

Q.

So that would – in your opinion, if the semaglutide made the diabetes worse, that would still meet claim 1 of the ‘462 patent?

A.

Yes. No level of efficacy is required, and so a negative effect, I guess, would still meet that claim. And I guess, as I think about this, I might add, I’m aware of treatments for a variety of conditions that do make the condition worse, not better. So that is in the realm of possibility, I would say.

EX2552 (Bantle Reply Dep. Tr.), 15:20-16:20; SurRep.2 n.2

Dr. Jusko

Q.

Okay. But in terms of your understanding of what the claim construction of the preamble means, would claim 1 be met if administering the semaglutide as claimed resulted in a statistically insignificant decrease in HbA1c?

A.

Probably not.

Q.

And why is that?

A.

Statistical significance is often a very small change that may or may not correspond to clinical significance. But treating diabetes requires clinically meaningful change.

EX2553 (Jusko Reply Dep. Tr.), 41:3-15; SurRep.1-2

Petitioner's Dr. Bantle Lacks Credibility

Dr. Bantle's Declaration

In my opinion, these dosing arms would indicate to a POSA that the optimal dose likely lay between 0.8 and 1.6 mg. A later version of the NCT773 protocol then tested a once weekly 0.8 mg dose with titration and a once weekly 1.2 mg dose with titration. EX1014 (NCT773) at 7 ("Last Updated on July 15, 2010"); see also, e.g., EX1003 (First Decl.) ¶¶ 140, 145, 259, 325. A POSA therefore would have been motivated to optimize the semaglutide dose between 0.8 mg and 1.6 mg (or 1.2 mg) once weekly, yielding a dose of 1.0 mg once weekly, because the titration protocol signaled a potential transition from lower doses where tolerability could be considered less of a factor, to higher doses where tolerability could be considered more of a factor. The once weekly 1.0 mg dose, sitting near what would appear to be the transition point, would appeal to a POSA as having a better balance between efficacy and side effects than other doses.

EX1300 (Bantle Reply Decl.), ¶266; SurRep.21

Dr. Bantle at Deposition

- Q. Would all of those doses have been optimized?
- A. ***I don't have an opinion about what dose is optimal.*** I simply have an opinion about what dose is obvious. And clearly, the 1.0 milligram dose was obvious.

EX2552 (Bantle Reply Dep. Tr.), 46:18-47:2; SurRep.21

Petitioner's Dr. Jusko Lacks Credibility

Dr. Jusko's Declaration

That the 0.8 mg dose was tested in NCT657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a skilled artisan would have been motivated to optimize the dose in that range to 1.0 mg. Moreover, the skilled artisan would have been motivated to use a dose between 0.8 mg and 1.6 mg, such as 1.0 mg, because the skilled artisan would have understood that Novo Nordisk may be apprehensive of the tolerability of 1.6 mg considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests doses lower than 1.6 mg and closer to 0.8 mg, such as 1.0 mg, would have a better balance between efficacy and side effects.

EX1301 (Jusko Reply Decl.), ¶267; SurRep.21

Dr. Jusko at Deposition

Q. And in your report, do you provide the opinion that 1 milligram is the optimal dose?

A. **I do not claim it as the optimum dose. It is a possible optimum dose. But 0.8, 0.9, 1.1 are also feasible.**

* * *

Q. Did you look at any efficacy and tolerability data to determine whether 1 milligram is an optimal dose?

A. **No, I did not.**

EX2553 (Jusko Reply Dep. Tr.), 25:6-27:10, 28:10-29:18; SurRep.21

The Numerous Uncited Paragraphs of Petitioner's Reply Expert Declarations Should Not Be Considered

- Other than to confirm deficiencies and inconsistencies with deposition testimony, the numerous uncited paragraphs of Petitioner's Reply expert declarations should not 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); SurRep.39

- For example, Petitioner did not cite:
 - Dr. Bantle (EX1300) paragraphs 6-12, 32-67, 71-73, 78-90, 113-122, 128-158, 171-181, 205-206, 221-226, 233, 245-258, 277-284, 286, 288-294, 322-364, 367-375;
 - Dr. Jusko (EX1301) paragraphs 4-12, 25-71, 76-90, 129-136, 180-182, 209, 227-234, 254-263, 281-284, 288-293, 296, 299-301, 304-353, 356-361;
 - Dr. Spiegel (EX1302) paragraphs 12-21, 40-134, 141-204, 209-218, 223-226, 228-251, 258-274, 278-284, 287-288, 290, 307-316;
 - Dr. Schwartzbard (EX1304) paragraphs 12-16, 32-73, 103-117, 146-149, 160-162;
 - Dr. Coca (EX1306) paragraphs 21-22, 32-105, 108-110, 112-114, 119-134, 145-150, 152-157, 160-164;
 - Dr. McDuff (EX1308) paragraphs 5-8, 17-28, 47-48, 59-69, 86-88, 92-93.