

***MYLAN PHARMACEUTICALS INC., DR. REDDY'S LABORATORIES, INC.,
DR. REDDY'S LABORATORIES, LTD., SUN PHARMACEUTICAL
INDUSTRIES LTD., AND SUN PHARMACEUTICAL INDUSTRIES, INC.,
Petitioners
v.
NOVO NORDISK A/S,
Patent Owner***

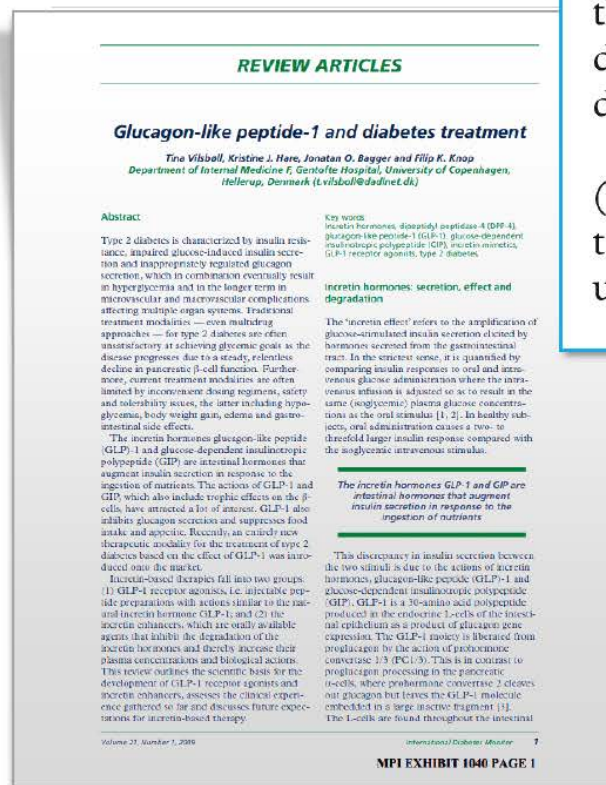
IPR2023-00724*

U.S. Patent No. 10,335,462

August 27, 2024

*IPR2024-00009 (Dr. Reddy's Laboratories) and IPR2024-00107 (Sun Pharmaceutical Industries)
have been joined with this proceeding

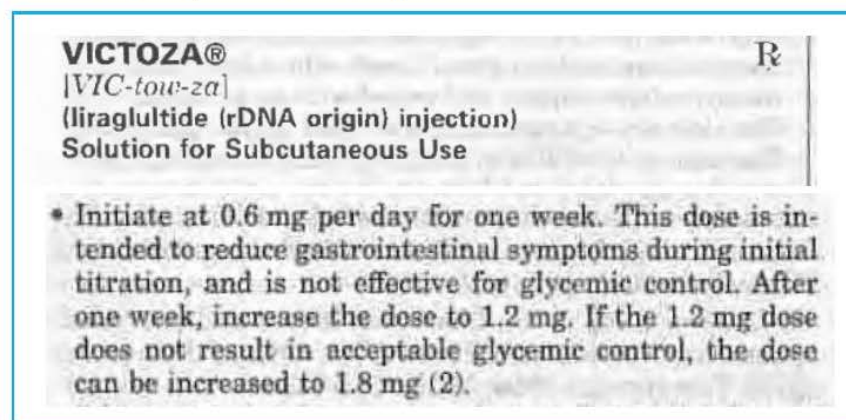
Background- Known GLP-1 Treatment of T2D



intake and appetite. Recently, an entirely new therapeutic modality for the treatment of type 2 diabetes based on the effect of GLP-1 was introduced onto the market.

Incretin-based therapies fall into two groups: (1) GLP-1 receptor agonists, i.e. injectable peptide preparations with actions similar to the natural incretin hormone GLP-1; and (2) the

Ex. 1040 at 1; Ex. 1003 at ¶¶ 71.



Ex. 1039 at 2;
Ex. 1003 at ¶¶ 74-75.

Background — Known GLP-1 Agonists and Actions

Table 1 | Incretin-based therapies

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

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

Ex. 1012 at 2-3.

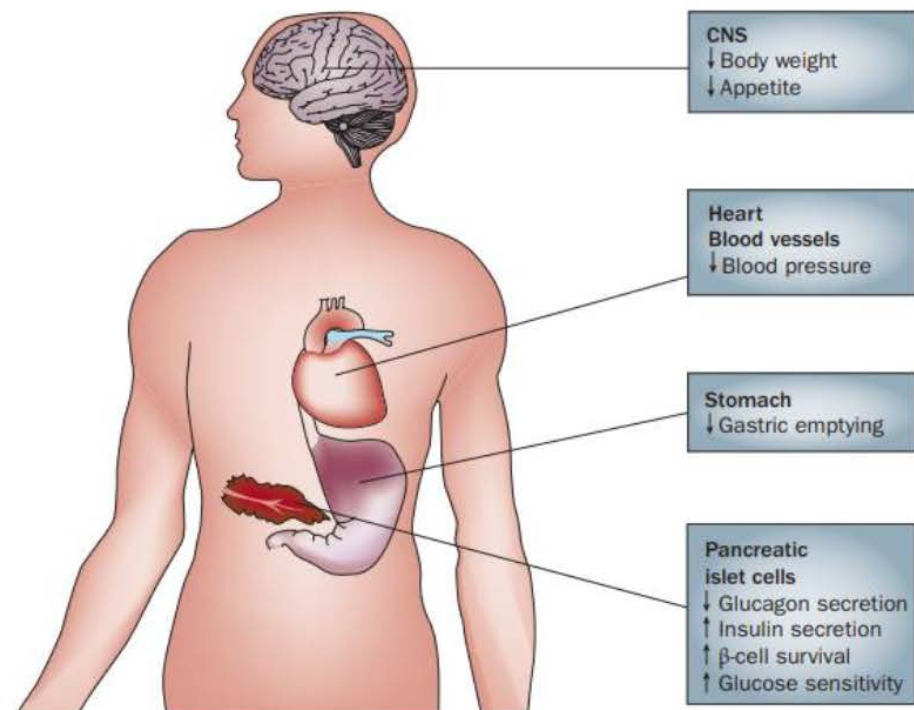


Figure 1 | GLP-1 receptor agonists exert diverse actions on distinct target tissues, which lead to reduction of blood glucose level and body weight in humans. Abbreviations: CNS, central nervous system; GLP-1, glucagon-like peptide 1.

Ex. 1012 at 2-3.

The '462 Patent

The invention relates to use of long-acting GLP-1 peptides in certain dosage regimes for the treatment of type 2 diabetes, obesity, etc.

Ex. 1001 at 1.

US910335462B2

(12) **United States Patent**
Jensen

(19) **Patent No.:** US 10,335,462
(41) **Date of Patent:** *Jul. 2, 2019

(54) **USE OF LONG-ACTING GLP-1 PEPTIDES**

(71) **Applicant:** Novo Nordisk A/S, Registered (DK)

(72) **Inventor:** Charlotte Bjærns Jensen, Charlottelund (DK)

(73) **Assignee:** Novo Nordisk A/S, Registered (DK)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

OTHER PUBLICATIONS

Studied S. et al. An Overview of once-weekly glimepiride period-1 receptor agonists available efficacy and safety data and perspective for the future, *Diabetes, Obesity and Metabolism* Year 2011, vol. 15, No. 5, pp. 394-407.

Haw. S. J. et al. Efficacy and safety of once-weekly semaglutide once daily in patients with type 2 diabetes (STEP 1): a randomised, open-label study, *Lancet*, 2018, vol. 391, pp. 1017-1026.

Kim et al. "Effects of Once-Weekly Dosing of a Long-Acting Glucagon-Like Peptide-1 Receptor Agonist on Glycemic Control and Body Weight in Patients with Type 2 Diabetes," *Diabetes Care* (2017) vol. 40, pp. 1447-1450.

Reference: NDA 202-230-010 Package Information, 1479 (Feb. 2018).

Clinical Trial NCT03099957 entitled "A Randomized Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide," pp. 1-5 Nov. 2017, accessed Sep. 26, 2019 at clinicaltrials.gov/ct2/show/study/NCT03099957 (2017, 11, 27).

Lee et al. "Semaglutide versus Once-Weekly Liraglutide in Type 2 Diabetes," *Diabetes Care* (2018) vol. 41, No. 10, pp. 1939-1946.

European Assessment Report, Eur. Med. Agency, pp. 6-14 (2014) accessed Sep. 26, 2019 at www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/022735/WC50010510.pdf.

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Minors et al. "The Role for GLP-1 in Regulation of Body Weight," *Progress in Molecular Biology and Translational Science*, 104, pp. 109-131 (2017).

Clin. Diabetes Health and Nutrition Conference Summary: Healthy Weight, Overweight and Obesity among U.S. adults," 10-12 Nov. 2017, accessed May 15, 2019 at www.gpi-nutrition.com/sites/default/files/healthy.pdf.

Field of Classification Search:
None
See application file for complete search history.

References Cited:

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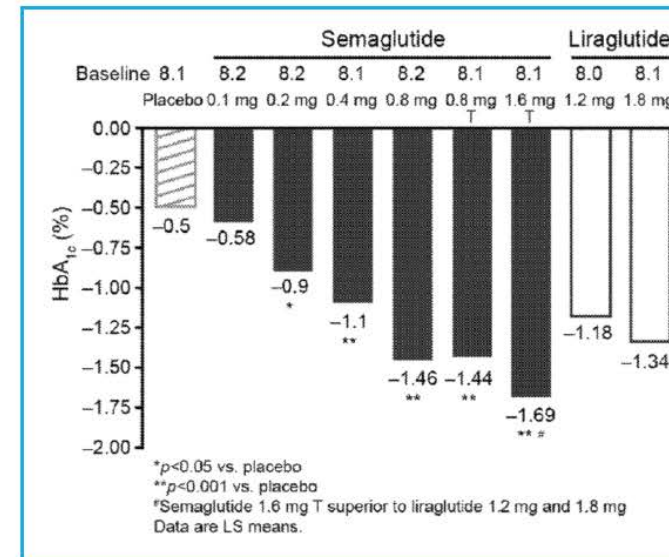
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EP 2401106 A2 1/2011

50 Claims, 6 Drawing Sheets
Specification includes a Sequence Listing.

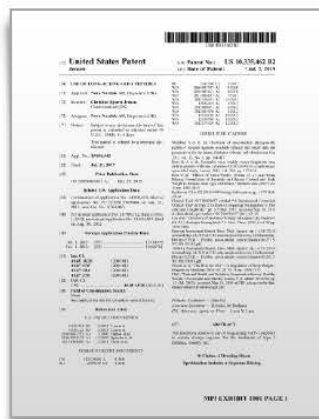
MPI EXHIBIT 1001 PAGE 1



Ex. 1001 (Fig. 1).

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

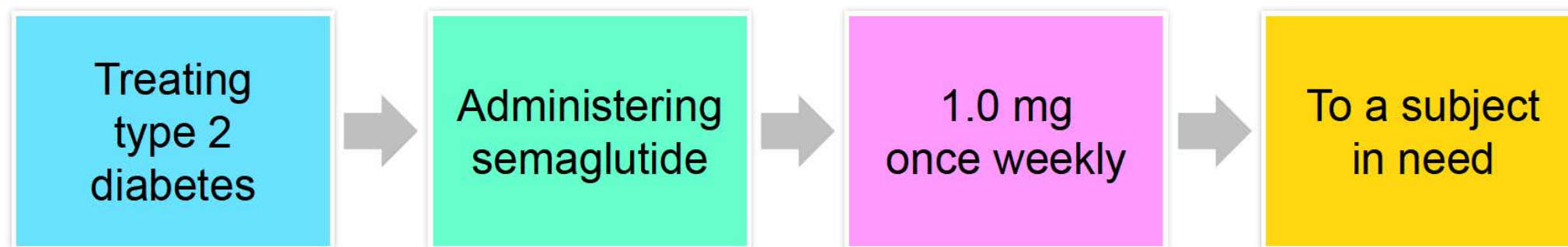
Claim 1 of '462 Patent



The invention claimed is:

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.

'462 patent (Ex.1001), claim 1 (annotated)



Claim 1 of '462 Patent: Preamble Construction

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 Board agreed with the parties that the preamble of claim 1 is limiting, and recites a limitation of administering semaglutide to a subject with type 2 diabetes.

See Paper 10 at 23.

- The Board also agreed with the parties “that the preamble does not require any particular level of efficacy.”

See Paper 10 at 23.

- The Board further “determine[d] that no further express claim construction of any claim term is necessary” for the '462 patent.

See Paper 10 at 23.

Grounds of Unpatentability

- 1.** Claims 1-3 of the '462 patent are anticipated by WO421 (Ex. 1011)
- 2.** Claims 1-3 of the '462 patent are anticipated by Lovshin (Ex. 1012)
- 3.** Claims 1-10 of the '462 patent would have been obvious over WO421 (Ex. 1011) in view of the '424 publication (Ex. 1016)
- 4.** Claims 1-10 of the '462 patent would have been obvious over WO537 (Ex. 1015) in view Lovshin (Ex. 1012)
- 5.** Claims 1-10 of the '462 patent would have been obvious over NCT657 (Ex. 1013) and NCT773 (Ex. 1014) in view of the '424 publication (Ex. 1016)

WO421 Is Prior Art

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

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A61K 35/02 (2006.01) A61P 3/06 (2006.01)
A61K 35/04 (2006.01)

(52) International Application Number
PCT/EP2011/057516

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(25) Filing Language
English

(26) Publication Language
English

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(54) Designated States (where indicated, for every
kind of regional protection available): AE, AU, AT, AM,
AX, AY, AZ, BA, BB, BG, BH, BR, BY, BZ, CA, CH, CL,
CN, CO, CR, CU, CZ, DE, DK, DM, DO, EC, EE, EG,
ES, FI, FO, FR, GB, GR, GT, HK, HN, HU, ID, IL, IN, IS,
JP, KE, KG, KH, KR, KZ, LA, LU, LV, LY, MA, MD, ME,
MG, MK, MN, MU, MV, MW, MX, MY, MZ, NA, NG, NI,
NO, NZ, OM, PA, PE, PG, PH, PK, PL, PT, RO, RU, SD, SE,
SG, SI, SK, SL, SM, ST, SV, SY, TH, TJ, TN, TR, TT, TZ,
UA, UG, US, UZ, VC, VN, ZA, ZM, ZW

(57) Abstract: The present invention relates to methods for treating and/or preventing metabolic diseases comprising the use
of a combination of a GLP-1 receptor agonist and a DPP-4 inhibitor.

MPI EXHIBIT 1011 PAGE 1

(22) International Filing Date:

5 May 2011 (05.05.2011)

(25) Filing Language:

English

(26) Publication Language:

English

Ex. 1011 at 1.

“(e) ... an international application ... shall have the effects for the purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published ...”

Pre-AIA 35 U.S.C. § 102(e).

Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen

*Apator Miitors Aps v.
Kamstrup A/S,*

887 F.3d 1293, 1295 (Fed. Cir. 2018)

“An inventor can swear behind a reference by proving he conceived his invention before the effective filing date of the reference and was diligent in reducing his invention to practice after that date.”

*REG Synthetic Fuels, LLC v.
Neste Oil Oyj,*

841 F.3d 954, 962 (Fed. Cir. 2016)
(citation omitted)

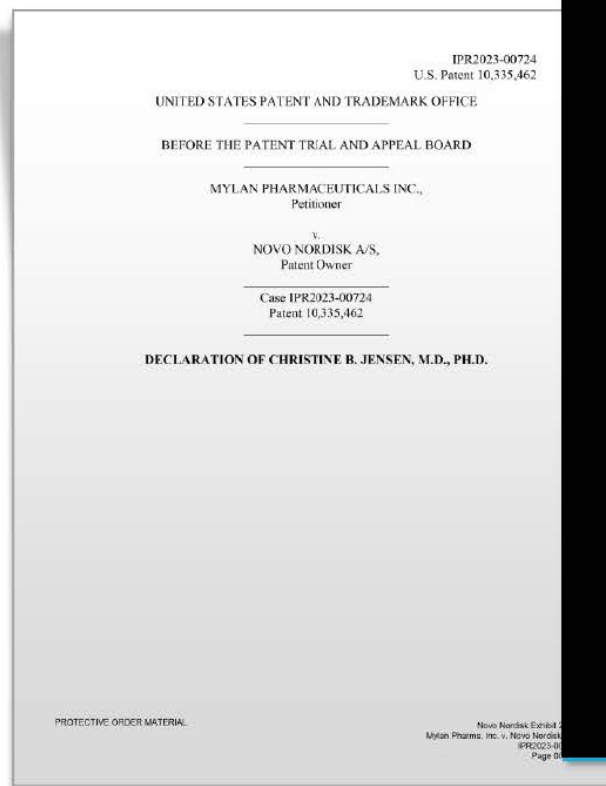
“Conception is ‘the formation, in the mind of the inventor of *a definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.*’”

*Burroughs Wellcome Co. v.
Barr Laby’s, Inc.,*

40 F.3d 1223, 1228 (Fed. Cir. 1994)
(citation omitted)

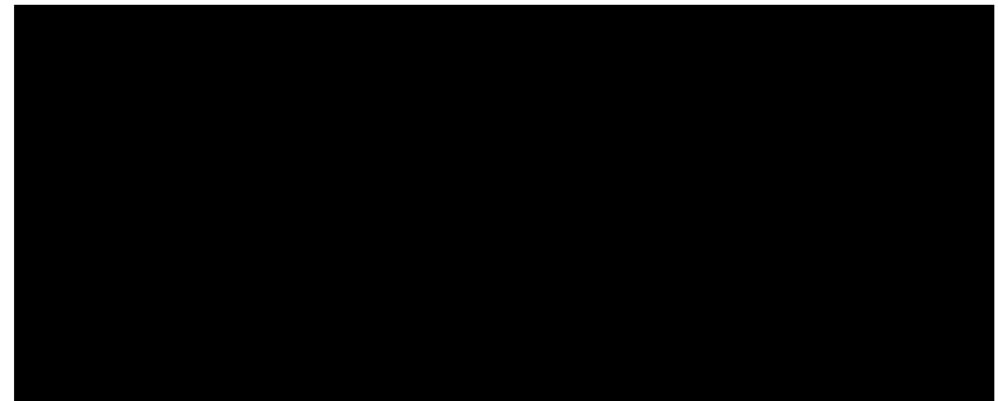
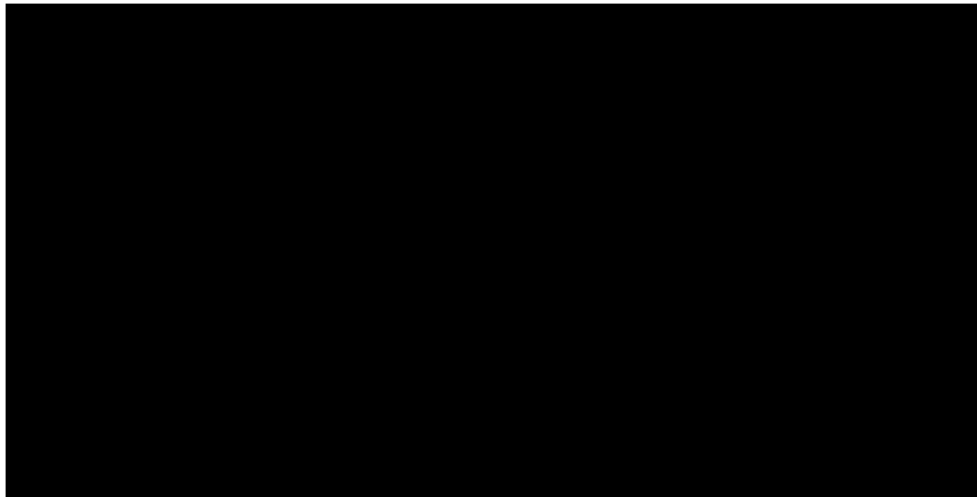
“But an inventor need not know that his invention will work for conception to be complete. He need only show that he had the idea; the discovery that an invention actually works is part of its reduction to practice.”

Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen

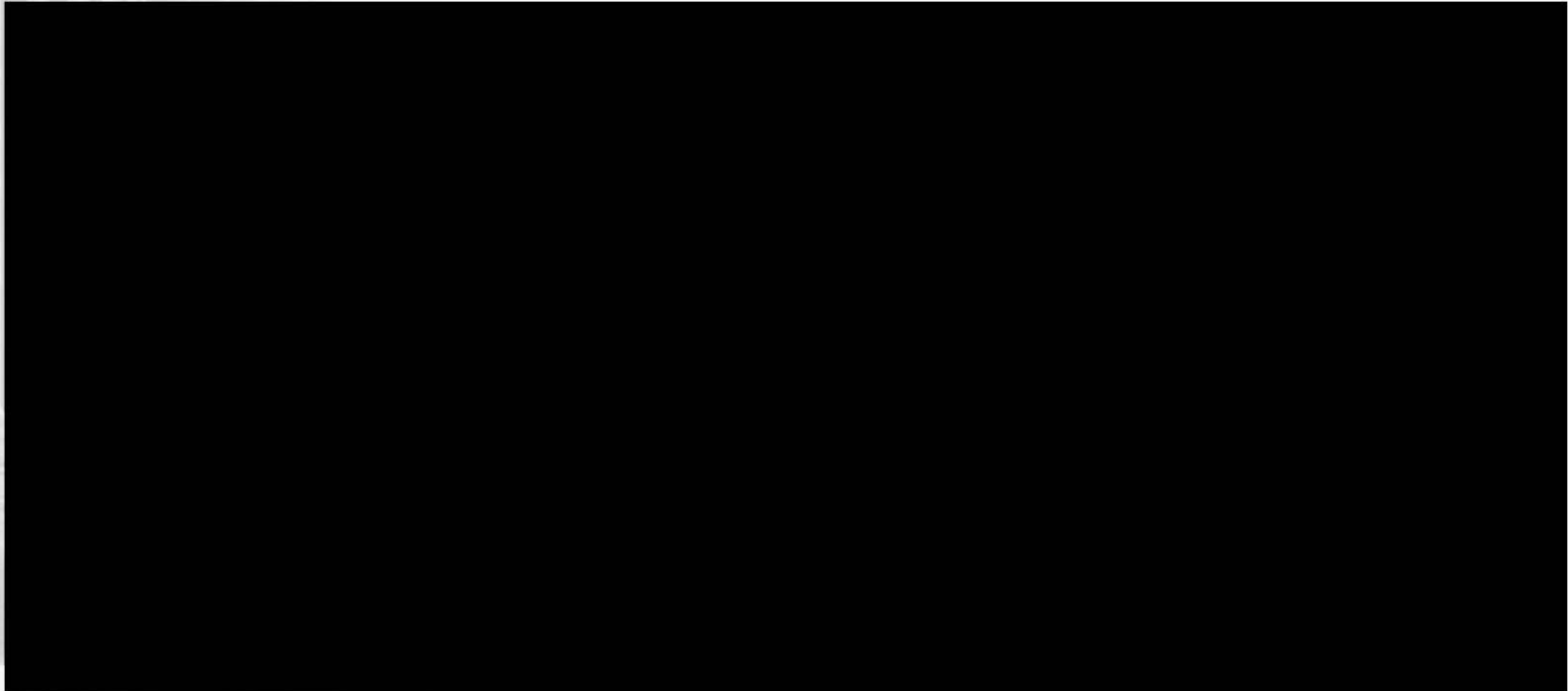


Ex. 2050, ¶ 21.

Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen



Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen



Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen

PO argues 1.0 mg dose communications “just a general goal”

PO Sur-Reply (citing *Creative Compounds* and *Dawson*).

Creative Compounds, LLC v. Starmark Laby's,
651 F.3d 1303, 1312 (Fed. Cir. 2011)

“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.’

* * *

In this email, Cornelius speculates that the method of making dicreatine malate ‘should’ be like that of making creatine citrate. The district court concluded, and this court agrees, that this email is insufficient to establish prior conception of the subject matter of the ’373 Patent. Creative failed to submit testimony explaining the significance of this email and whether this reference would constitute conception of subject matter within the scope of even a single claim in the ’373 Patent.”

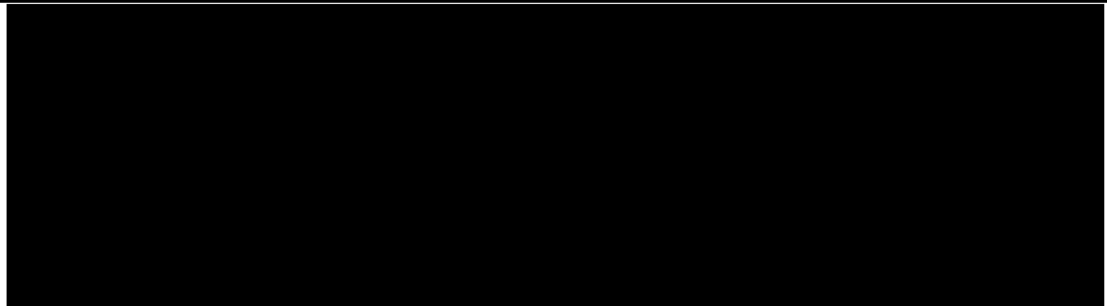
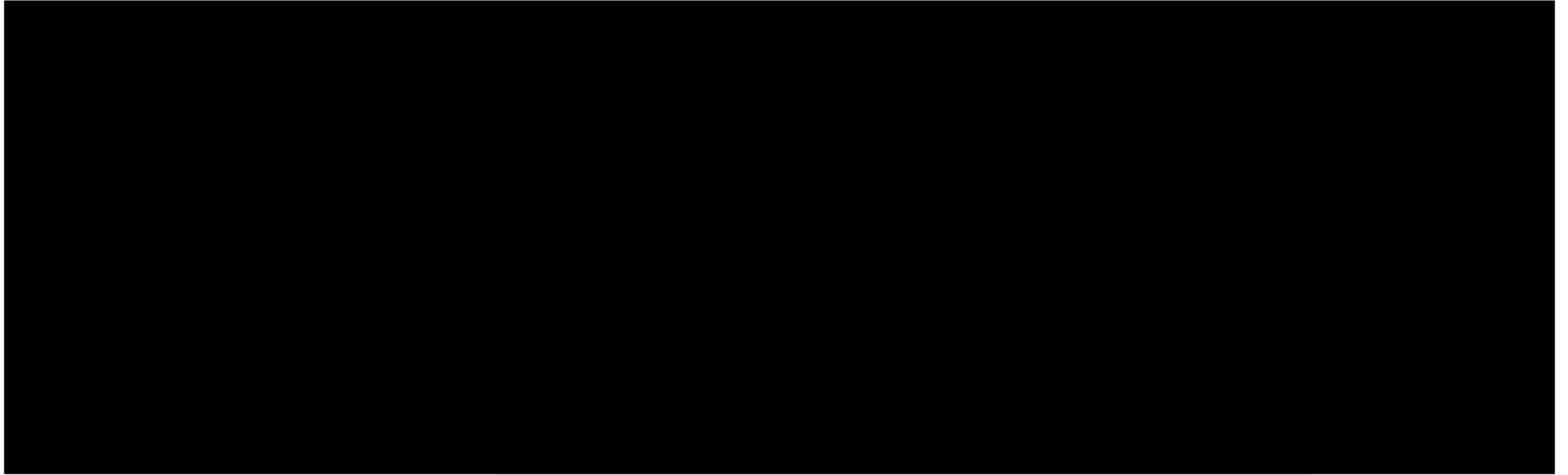
Dawson v. Dawson,
710 F.3d 1347, 1353 (Fed. Cir. 2013)

“A ‘preliminary’ statement about a ‘possibility’ or ‘potential use,’ alongside a recommendation for continued work and a ‘report back’ in the future, falls short of a ‘definite and permanent idea of the complete and operative invention, as it is hereafter to be applied in practice.’

The inadequacy of UCSF’s showing is equally clear in the context of the specific interference counts. The limitations of the ‘719 count include specific concentrations, such as ‘0.01% to 1.0% of an azalide antibiotic’ and ‘0.1 to 10% of a polymeric suspending agent’ which is a water-swelling water-insoluble cross-linked carboxy-vinyl polymer which comprises at least 90% acrylic acid monomers and 0.1% to 5% cross-linking agent.’ As the Board found, UCSF failed to provide ‘evidence to suggest a complete conception of th[at] specific formulation.’”

Patent Owner Did Not Antedate WO421: No Corroboration

Evidence pre-dating alleged conception



POR 15; Pet. Reply 3;
PO Sur-Reply 7; Ex. 2050, ¶ 21

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

Patent Owner Did Not Antedate WO421: No Corroboration

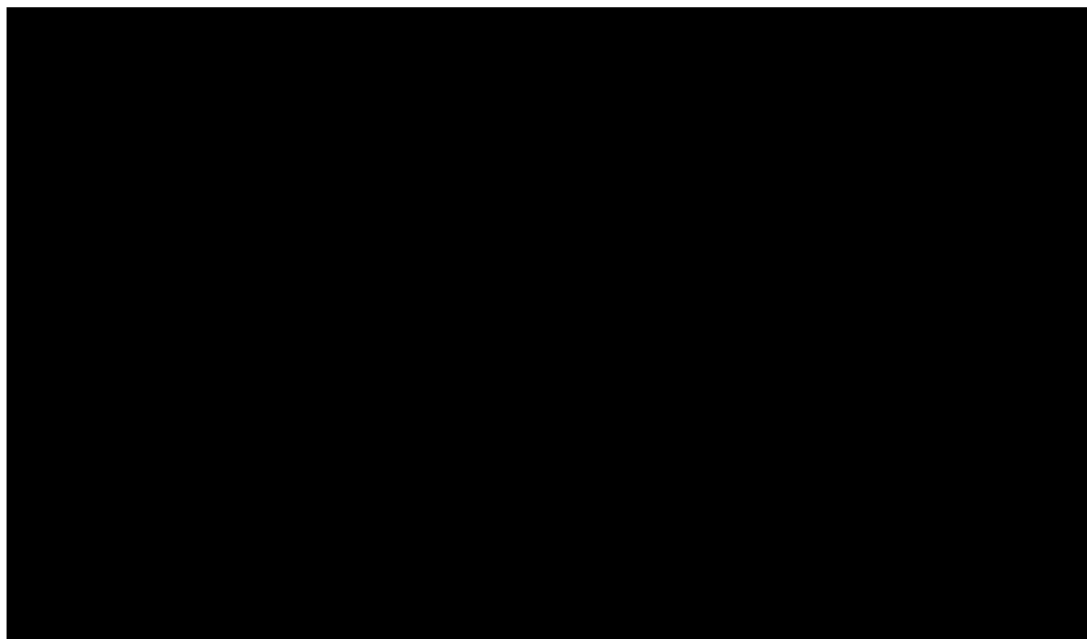
Evidence post-dating alleged conception:

[REDACTED]

[REDACTED]

Patent Owner Did Not Antedate WO421: No Corroboration

Evidence post-dating alleged conception: [REDACTED]



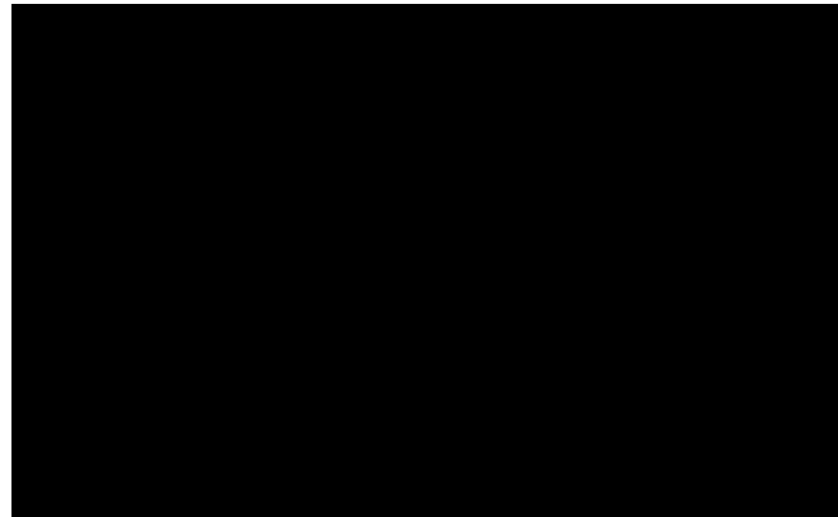
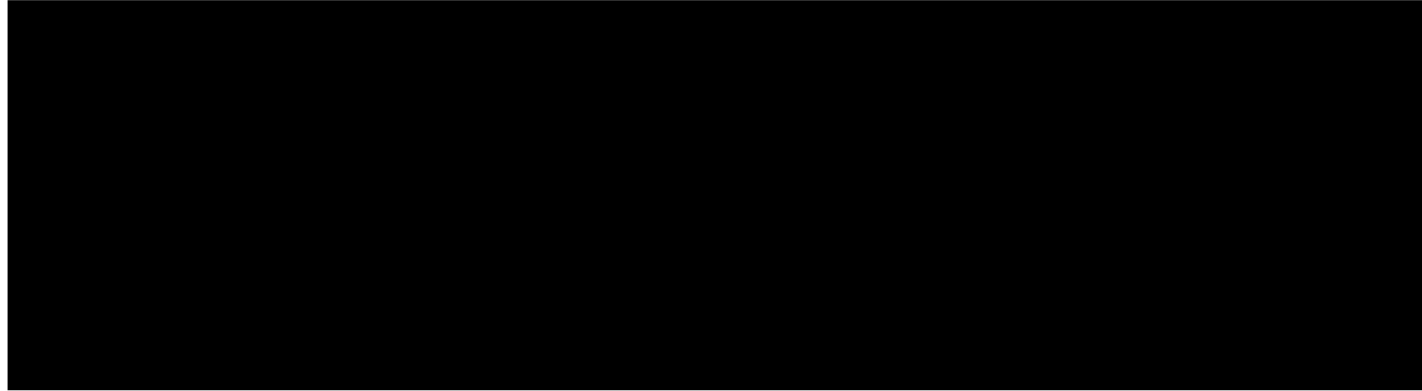
NFC Tech., LLC v. Matal,

871 F.3d 1367, 1373 (Fed. Cir. 2017) (citations omitted)

“Although the Board gave the sheet little weight due to the lack of detail relating to what Charrat directed CE to fabricate, the cover sheet still corroborates Charrat’s account in significant respects. For example, the cover sheet was sent to ‘B. CHARRAT’ at ‘Inside’ on September 10, 1998 with ‘M210H’ in the subject line. The date corroborates Charrat’s testimony that he sent the prototype to fabrication in early September 1998. In response to the cover sheet, Charrat wrote ‘OK FAB’ and signed his last name underneath it. Charrat’s approval was also dated September 10, 1998—that is, the same day that CE sent the cover sheet to him. That the cover sheet was sent to and approved only by Charrat also corroborates that it was he who directed the project and communicated the design for fabrication to CE.”

Patent Owner Did Not Antedate WO421: No Corroboration

Evidence post-dating alleged conception:



Ground 1:

WO421 Anticipated Claims 1-3

WO421 Disclosed All Elements of Claim 1



The invention claimed is:

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.

'462 patent (Ex.1001), claim 1 (annotated)

WO421 Disclosed All Elements of Claim 1

Method for treating type 2 diabetes

Treating type 2 diabetes



The present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic

Ex. 1011, 2:4-5.

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Ex. 1011, 65:26-31.

Pet. 26-28;
Ex. 1003, ¶¶ 233-234; Ex. 1005, ¶¶ 180-183

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

20
MPI EXHIBIT 1334 PAGE 20

WO421 Disclosed All Elements of Claim 1

Method for treating type 2 diabetes

Treating type 2 diabetes

- *Duke Univ. v. BioMarin Pharm. Inc.*, 685 F. App'x 967, 973 (Fed. Cir. 2017) (“proof of efficacy or an actual reduction to practice...is not required for a reference to be an anticipation of...method of treatment claims”);
- *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005) (same);
- *Bristol-Myers Squibb Co. v. Ben Venue Lab'ys, Inc.*, 246 F.3d 1368, 1379 (Fed. Cir. 2001) (“[A]nticipation does not require actual performance of suggestions in a disclosure. Rather, anticipation only requires that those suggestions be enabling to [a POSA].”).

WO421 Disclosed All Elements of Claim 1

Administering semaglutide

Administering Semaglutide

15 The present invention further relates to a method for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined (e.g. simultaneous, separate or sequential) administration of an effective amount of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) as defined herein and of an effective amount of a DPP-4 inhibitor as defined herein to the patient (particularly human patient) in need thereof, such as e.g. a
20 patient as described herein.

Ex. 1011, 11:14-20.

20 Preferred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide.

Ex. 1011, 34:20-22.

WO421 Disclosed All Elements of Claim 1

Administering semaglutide

Administering Semaglutide

235. In my opinion, WO421's specification also disclosed the claim element "comprising administering semaglutide." With respect to this claim element, WO421 disclosed that "[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide." *Id.* at 34:20-22 (emphasis added); *see also id.* at 65:27-31 (claim 17, reciting in relevant part, "[a] GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both" (emphasis added)). A POSA would have understood from these passages that WO421 disclosed the use of semaglutide in a method "for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus."

* * *

247. In my opinion, therefore, WO421's specification disclosed the element "comprising administering semaglutide" in claim 1 of the '462 patent.

184. *Second*, WO421 also disclosed the element "comprising administration of semaglutide" of claim 1. It is my understanding from counsel that the term "comprising" means that the claim limitations that follow the term "comprising" must be present in an embodiment of the claims, but that the term is "open," meaning

* * *

188. Moreover, because the scope of "[a] method for treating type 2 diabetes, *comprising* administering semaglutide" in claim 1 of the '462 patent may include administering semaglutide before, after, or with other drugs, the specification and claim 17 of WO421 disclosed the element "comprising administration of semaglutide" of claim 1.

A POSA would have understood this to include administering semaglutide alone. Ex. 1003, ¶¶ 235-255; Ex. 1005, ¶¶ 184-188.

WO421 Disclosed All Elements of Claim 1

Administering semaglutide

Administering Semaglutide

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Ex. 1011, 65:26-31

WO421 Disclosed All Elements of Claim 1

Administering semaglutide

Administering Semaglutide

- '462 patent recites “comprising”

Ex. 1001, 35:42-44.

- Claim is open and allows for other components

Medichem, S.A. v. Rolabo, S.L., 353 F.3d 928, 933 (Fed. Cir. 2003) (holding “comprising” in a claim allows for additional method steps); *Invitrogen Corp. v. Biocrest Mfg., L.P.*, 327 F.3d 1364, 1368 (Fed. Cir. 2003) (same); *Lucent Techs., Inc. v. Gateway, Inc.*, 525 F.3d 1200, 1214 (Fed. Cir. 2008) (holding “comprising” means method steps are essential but other steps may be added).

- Claim 1 therefore allows administering additional therapeutics with semaglutide, and WO421 thus discloses administering semaglutide even if disclosed as a co-administered option

See *Invitrogen*, 327 F.3d at 1368; see also *In re Capsule Techs., Inc.*, 759 F. App'x 975, 980 (Fed. Cir. 2019) (where claim language read “a synthetic capsule construct...comprising,” anticipation could not be defeated by showing prior art contained additional material in capsule beyond components described in the claim after “comprising”); Ex. 1011; Ex. 1003, ¶¶ 238-241; Ex. 1005, ¶¶ 184-188.

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

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

Ex. 1011, 44:13.

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Ex. 1011, 65:26-31.

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

264. Additionally, WO421's claim 17 disclosed the claim element "once weekly in an amount of 1.0 mg." WO421's claim 17 recites "[a] *GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.*" Ex. 1011 (WO421) at 65:27-31 (emphasis added).

* * *

266. In my opinion, therefore, at least WO421's claim 17 also disclosed the claim element "once weekly in an amount of 1.0 mg" recited in claim 1 of the '462 patent.

Ex. 1003, ¶¶ 264-266.

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

189. *Third*, WO421 also disclosed the element “once weekly in an amount of 1.0 mg.” In particular, the specification of WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1 to 1.6 mg).” *Id.* at 44:14. In my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. *See* Ex. 1039 (Victoza label) at 2. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg,

192. Moreover, because claim 17 of WO421 recited “[a] GLP-1 receptor agonist selected from . . . semaglutide . . . for use in a method of treating type 2 diabetes . . . said method comprising administration . . . of the GLP-1 receptor agonist,” a POSA would immediately envision using the once weekly dose of “0.1 to 1.6 mg” semaglutide disclosed in WO421 for administration for at least the same reasons as described above. Thus, claim 17 of WO421 also disclosed the element “once weekly in an amount of 1.0 mg” of claim 1.

Ex. 1005, ¶¶ 189-192.

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

WO421 range not limited to specific NCT657 doses

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

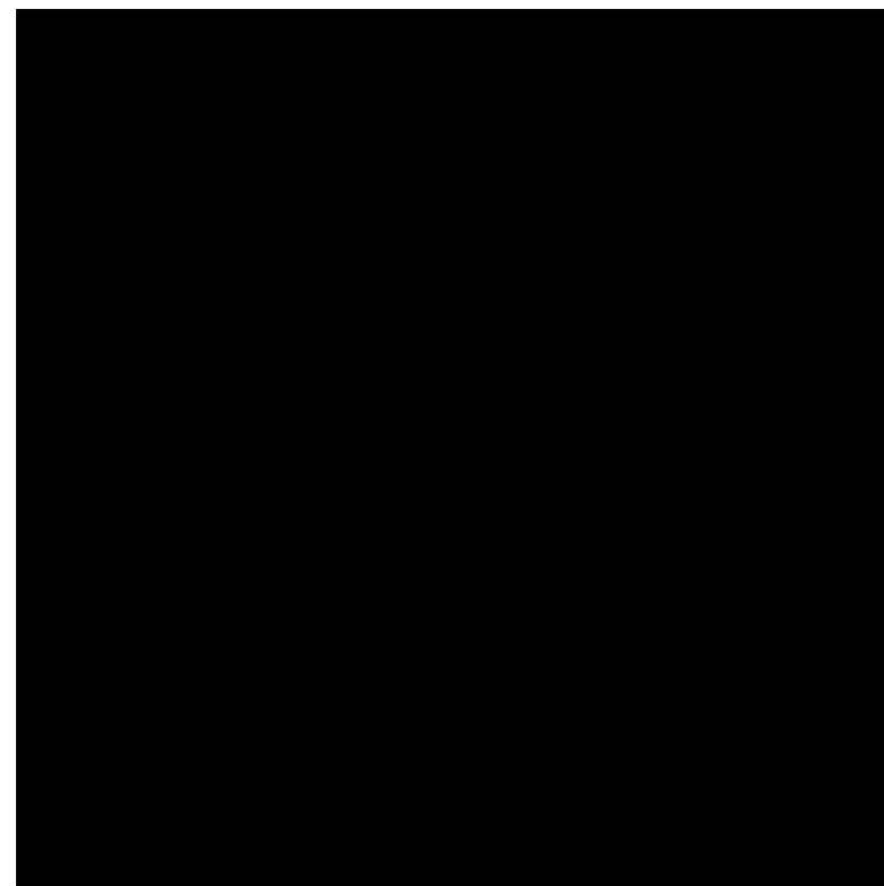
Inst. Dec. at 37.

Q. Is it your opinion that a POSITA would have looked to NCT657 to understand the scope of the dose range disclosed by WO421?

MS. GREB: Object to form.

A. Well, in my opinion, they affirmed each other. You get the same dose range from two different sources.

Ex. 2018 (71:5-11) (Bantle Dep.).



WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

PO's 1-in-320 theory conflicts with claim 1: "1.0" mg covers 1/16 of WO421's range

233. Thus, in my opinion, POSITA would have recognized that WO421's disclosed "range" encompasses at least 320 possible doses and would not have understood WO421 as disclosing administration of once-weekly semaglutide at every one of those at least 320 doses, or at once envisaged from WO421 the administration at the claimed 1.0 mg once-weekly dose (which would have been only 1 of 320 possible doses in that range).

Ex. 2010 (Rosenstock Dec.), ¶ 233.

Q Did you actually form an opinion in your report about how broadly the claim term 1.0 milligrams would be interpreted in this case?

A No. I just specifically asked for the 1.0 milligram, that that was in the claim 1.

Ex. 1313 (235:14-18) (Rosenstock Dep.).

Viskase Corp. v. Am. Nat'l Can Co.,
261 F.3d 1316, 1320 (Fed. Cir. 2001)

"[1] The district court construed the density term 'about 0.91 g/cm³' to mean densities between 0.905 and 0.914, based on the reasoning that numbers in this range would be rounded to 0.91. We agree that this is a standard scientific convention when a number has not been carried to the next mathematically significant figure."

AstraZeneca AB v. Mylan Pharms. Inc.,
19 F.4th 1325, 1342 (Fed. Cir. 2021) (Taranto, J. dissenting)

"Under this ordinary-meaning approach, the significant-figure interval meant by '0.001%' is 0.0005% to 0.0014%, based on rules of rounding and the single significant figure at the third decimal place."

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

1.0 mg is not “critical”

Q And it reports that, In the full analysis set, semaglutide, greater than or equal to 0.2 milligrams, dose-dependently reduced HbA_{1c} from baseline, Figure 1, and increased the likelihood of achieving HbA_{1c} less than 7 percent, correct?

A That's what it says.

* * *

My question to you is, is the 0.8 milligram dose, in your opinion, based on the data in the patent specification critical?

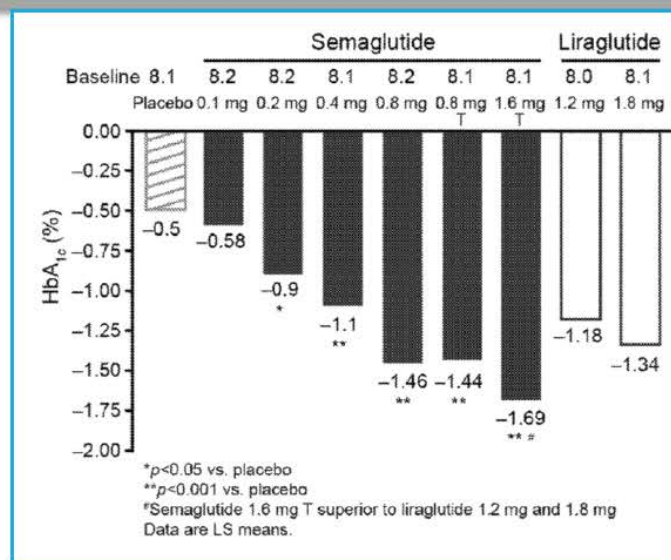
* * *

A I think I did, Counsel. I already mentioned that the dosages from 0.1 to 1.6 are different. And my understanding is that meets the criticality.

Ex. 1313 (153:13-18; 163:13-15; 164:1-4)
(Rosenstock Dep.).

Genentech, Inc. v. Hospira, Inc.,
946 F.3d 1333, 1338 (Fed. Cir. 2020) (citation omitted)

“Once the patent challenger has established, through overlapping ranges, its prima facie case of anticipation, ‘the court must evaluate whether the patentee has established that the claimed range is critical to the operability of the claimed invention.’”



Ex. 1001 (Fig. 1).

WO421 Disclosed All Elements of Claim 1

To a subject in need thereof

To a Subject in Need

35 In one embodiment, diabetes patients within the meaning of this invention may include patients who have not previously been treated with an antidiabetic drug (drug-naïve patients). Thus, in an embodiment, the therapies described herein may be used in naïve patients. In another embodiment, diabetes patients within the meaning of this invention may include patients with advanced or late stage type 2 diabetes mellitus (including patients with failure to conventional antidiabetic therapy), such as e.g. patients with inadequate glycemic control on one, two or more conventional oral and/or non-oral antidiabetic drugs as defined herein, such as e.g. patients with insufficient glycemic control despite (mono-)therapy with

15 A further embodiment of diabetic patients within the meaning of this invention refers to patients ineligible for metformin therapy including

- patients for whom metformin therapy is contraindicated, e.g. patients having one or more contraindications against metformin therapy according to label, such as for example patients with at least one contraindication selected from:

20 renal disease, renal impairment or renal dysfunction (e.g., as specified by product information of locally approved metformin),

Ex. 1011, 8:35-10:7.

Pet. 34-35; Ex. 1003, ¶¶ 267-268;
Ex. 1005, ¶¶ 193-195

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

32

MPI EXHIBIT 1334 PAGE 32

WO421 Disclosed All Elements of Claim 1

To a subject in need thereof

To a Subject in Need

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g.
30 separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Ex. 1011, 65:26-32

WO421 Disclosed All Elements of Claim 1

To a subject in need thereof

To a Subject in Need

**POSA would have recognized “administration”
was necessarily to a subject in need of such treatment.**

269. Claim 17 of WO421 does not expressly recite the language “to a subject in need thereof,” but it does recite that the GLP-1 receptor agonist was “for use in a method of treating type 2 diabetes.” *Id.* at 65:27-31. A POSA would have understood the disclosure of treating type 2 diabetes to include inherently a patient in need of such treatment, because type 2 diabetes occurs in a patient. Therefore claim 17 of WO421 also disclosed the “to a subject in need thereof” claim limitation.

Ex. 1003, ¶ 269.

193. *Fourth*, WO421 disclosed the element “to a subject in need thereof.” Throughout the disclosure, WO421 taught that the therapy should be for the treatment of diabetes in a human patient. *See, e.g.*, Ex. 1011 (WO421) at 37:3-5. The WO421 also disclosed that therapies “may be used in [drug] naïve patients,” or “patients with advanced or late-stage type 2 diabetes” or “patients ineligible for metformin” or “patients having...renal disease [or] ... disfunction.” *Id.* at 9:35-11:7. Thus, WO421 disclosed the element “to a subject in need thereof” of claim 1.

* * *

195. Thus, for the aforementioned reasons, both the specification and claim 17 of WO421 anticipated claim 1 of the '462 patent.

Ex. 1005, ¶¶ 193-195.

WO421 Disclosed All Elements of Claims 2 and 3

Method for treating type 2 diabetes



The invention claimed is:

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.

'462 patent (Ex.1001), claim 1 (annotated)

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.

'462 patent (Ex. 1001), claims 2 and 3.

WO421 Disclosed the Parenteral Element of Claim 2

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

Ex. 1011, 44:13

272. As of the priority date of the '462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump. Ex. 1034 (Knudsen patent) at 170:25-29. Therefore, a POSA would have understood that the “subcutaneous injection” disclosed in WO421 is a type of parenteral administration of a solution.

Ex. 1003, ¶ 272.

197. WO421 disclosed “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” Ex. 1011 (WO421) at 44:13. In my opinion, skilled artisans would have known that subcutaneous injection is a type of parenteral administration. *See, e.g.*, Ex. 1015 (WO537) at 35:15-16 (“Parenteral administration may be performed by subcutaneous . . . injection.”).

Ex. 1005, ¶ 197.

WO421 Disclosed the Subcutaneous Injection Element of Claim 3

200. WO421 disclosed “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” Ex. 1011 (WO421) at 44:13. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

Ex. 1005, ¶ 200.

272. As of the priority date of the ’462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump. Ex. 1034 (Knudsen patent) at 170:25-29. Therefore, a POSA would have understood that the “subcutaneous injection” disclosed in WO421 is a type of parenteral administration of a solution.

Ex. 1003, ¶ 272.

’462 claim 3 requires “the *solution* is administered by *subcutaneous* injection.” EX1001, claim 3. WO421 does not disclose a solution, EX2010, ¶262,

POR at 36.

Injectable formulations of the GLP-1 receptor agonists of this invention may be prepared according to known formulation techniques, e.g. using suitable liquid carriers, which usually comprise sterile water, and, optionally, further additives e.g. for aiding solubility or for preservation or the like, to obtain injectable solutions or suspensions.

Ex. 1011 (40:23-26).

Ground 2:

Lovshin Anticipated Claims 1-3

Lovshin Disclosed All Elements of Claim 1



The invention claimed is:

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.

'462 patent (Ex.1001), claim 1 (annotated)

Lovshin Disclosed All Elements of Claim 1

treating type 2 diabetes / administering semaglutide / to a subject in need

Treating
type 2
diabetes



Administering
semaglutide



1.0 mg
once weekly



To a subject
in need

Incretin-based therapies for type 2 diabetes mellitus

Julie A. Lovshin and Daniel J. Drucker

Abstract | Incretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus. These agents regulate glucose

Ex. 1012 at 1.

Continuous, subcutaneous administration of native GLP-1 to patients with type 2 diabetes mellitus (T2DM) lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss.¹⁰

Ex. 1012 at 1.

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.

Ex. 1012 at 5.

269. As with WO421, in my opinion, POSITA would have looked to publications regarding ongoing trials of NN9535, such as NCT657, to understand the doses within the range Lovshin mentions.

Ex. 2010 (Rosenstock Dec.), ¶ 269.

Lovshin Disclosed All Elements of Claim 1

1.0 mg once weekly

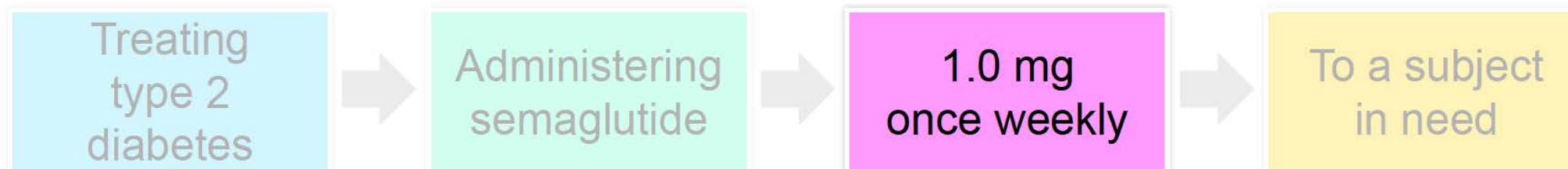


Table 1 | Incretin-based therapies

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

Ex. 1012, 2 (Table 1).

- Lovshin taught POSAs a narrow range of once-weekly doses of 0.1-1.6 mg of semaglutide were already being tested in clinical trials.

Ex. 1003, ¶ 360; Ex. 1005, ¶¶ 252-255; Ex. 1012, 2 (Table 1).

- Prior art need not include proof of efficacy or actual performance--it need only be enabling to POSAs.

Bristol-Myers Squibb Co. v. Ben Venue Labs, Inc., 246 F.3d 1368, 1379 (Fed. Cir. 2001); *Rasmusson v. SmithKline Beecham Corp.*, 413 F.3d 1318, 1326 (Fed. Cir. 2005).

Lovshin Disclosed the Elements of Claims 2 & 3: parenteral / subcutaneous injection

Incretin-based therapies for type 2 diabetes mellitus

Table 1 | Incretin-based therapies

Agent	Dose	Status
GLP-1R agonists (subcutaneous injection)		

Ex. 1012 at 2.

311. As of the priority date of the '462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump. Ex. 1034 (Knudsen patent) at 170:25-29. Therefore, a POSA would have understood that the “subcutaneous injection” disclosed in Lovshin is a type of parenteral administration, and it would have been injection of a solution.

Ex. 1003, ¶ 311.

218. Lovshin disclosed that the dose of NN9535 (semaglutide) to be administered to a patient is “0.1–1.6 mg once weekly,” given by “subcutaneous injection” to treat type 2 diabetes. Ex. 1012 (Lovshin) at 2. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

Ex.1005, ¶ 218.

Obviousness of Claims 1-10

The Case for Obviousness

- Claims are *prima facie* obvious (claimed dose falls within a narrow prior art range), OR
- POSA would have been
 - Motivated to pursue a 1.0 mg dose,
 - WO421, Lovshin, and clinical trials taught treating T2D with 0.1 – 1.6 mg once weekly semaglutide
 - Active trials showed data supported safety and efficacy of the range
 - Evaluate doses in narrow range using known techniques
 - With a reasonable expectation of success
 - Clinical trial design principles taught characteristics of narrow range
 - Liraglutide, predecessor molecule, well studied and already approved

All Three Obviousness Combinations Disclose Using Once-Weekly Semaglutide to Treat T2D in an Identical Dose Range of 0.1 – 1.6 mg

WO421

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

* * *

17) A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Lovshin

Incretin-based therapies for type 2 diabetes mellitus

Table 1 | Incretin-based therapies

Agent	Dose	Status
<i>GLP-1R agonists (subcutaneous injection)</i>		
Exenatide	5–10 µg twice daily	A
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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

Ex. 1011 at 44, 65

NCT657

A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide

This study has been completed.

First Received on June 11, 2008. Last Updated on March 16, 2011 [History of Changes](#)

Sponsor:	Novo Nordisk
Information provided by:	Novo Nordisk
ClinicalTrials.gov Identifier:	NCT00696857

* * *

This trial was conducted in Europe, Asia and Africa. Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW, 1.5 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

Condition	Intervention	Phase
Diabetes Mellitus, Type 2	Drug: semaglutide Drug: placebo Drug: liraglutide	Phase II

* * *

Official Title: Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or Controlled With Diet and Exercise A 12 Week Multi-centre, Multi National, Double-blind, Placebo-controlled, Randomised, Nine Armed Parallel Group, Dose Finding Trial

Ex. 1013 at 15

Ex. 1012 at 1, 2

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

45

The '462 Patent Claims Are *Prima Facie* Obvious

***Galderma* involved a discrete point
disclosed in a prior art range**

Galderma Laby's, L.P. v. Tolmar Inc.,
737 F.3d 731, 736 (Fed. Cir. 2013)

“At the time of the invention, adapalene was a known compound and the prior art Shroot patents disclose topical adapalene compositions for the purpose of treating acne in a preferred range of 0.01%–1%, including several exemplary formulations containing adapalene in various concentrations. The asserted claims are directed to 0.3% topical adapalene compositions for the treatment of acne, which fall within the concentration range disclosed in the Shroot patents.”

Semaglutide Dosing Was a Result-Effective Variable

Prior art taught T2D treatment with a range of semaglutide doses and dose-finding trials were ongoing with different doses across the known range

NCT657

Arms	Assigned Interventions
A: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.1 mg, once weekly, s.c. injection
B: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.2 mg, once weekly, s.c. injection
C: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.4 mg, once weekly, s.c. injection
D: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.8 mg, once weekly, s.c. injection
E: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.8 mg with titration, once weekly, s.c. injection
F: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 1.6 mg with titration, once weekly, s.c. injection

NCT773

A: Experimental	Drug: NN9535 0.1 mg once weekly, s.c. injection
B: Experimental	Drug: NN9535 0.2 mg once weekly, s.c. injection
C: Experimental	Drug: NN9535 0.4 mg once weekly, s.c. injection
D: Experimental	Drug: NN9535 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks, s.c. injection
E: Experimental	Drug: NN9535 0.8 mg once weekly, s.c. injection
F: Experimental	Drug: NN9535 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.6 mg once weekly for 6 weeks, s.c. injection
G: Experimental	Drug: NN9535 S.c. injection: 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, followed by once weekly injections for 6 weeks. Dose to be determined based on safety and tolerability of previous dose steps. This dose-arm is optional and will only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.

In re Applied Materials, Inc.
692 F.3d 1289, 1297 (Fed. Cir. 2012)

“A recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective.”

Pet. 40-41; Pet. Reply 24-25; Ex. 1013 at 15-16, 19-20;
Ex. 1014 at 7, 11; Ex. 1003 ¶¶ 259, 399-401; Ex. 1005 ¶¶ 227-236

Semaglutide Dosing Was a Result-Effective Variable

Establishing that a variable is result-effective is a low bar

E.I. DuPont de Nemours & Co. v. Synvina C.V.

904 F.3d 996, 1009 (Fed. Cir. 2018)

The “situation where a ‘parameter optimized was not recognized to be a result-effective variable’ [is] an ‘exception’ ... [and] [o]ur subsequent cases have confirmed that this exception is a narrow one. Indeed, we have located no case where this court relied on a variable not being result-effective in an obviousness analysis.”
(citation omitted)

POSAs Were Motivated to Optimize in the Known Prior Art Dose Range

Petitioner's obviousness grounds do not require modifying any reference

Genentech, Inc. v. Hospira, Inc.,
946 F.3d 1333, 1341 (Fed. Cir. 2020)

“The normal desire of scientists or artisans to improve upon what is already generally known provides the motivation to determine where in a disclosed set of ... ranges is the optimum combination.” (citation omitted)

POSAs Were Motivated to Optimize in the Known Prior Art Dose Range

The semaglutide prior art dose range is not especially broad

E.I. DuPont de Nemours & Co. v. Synvina C.V.

904 F.3d 996, 1011 n.15 (Fed. Cir. 2018)

“We are not persuaded by Synvina’s argument that our decision in *Genetics Institute* supports not applying the burden-shifting framework. That case involved disclosure of very broad ranges in the prior art—68,000 variants of a protein made up of 2,332 amino acids—that did not invite routine optimization. In contrast, this case presents ‘not especially broad’ ranges of temperature and pressure.” (citation omitted)

PO Motivation to Combine Arguments Misapply the Law

“optimum.” *Id.* But Petitioner’s expert concedes: “I don’t think there’s any data to suggest what the optimized dose is.” EX2018, 108:16-109:15; EX2010, ¶319.

POR at 49
(citing Ex. 2018, 108:16-109:15,
asking Dr. Bantle “whether it’s your opinion that the 1-milligram
weekly dose of semaglutide is the optimized dose”)

Rep.20. But Petitioner’s experts had no reasoned basis to conclude any “range”
would be understood as limited to 16 doses (§II.A.2),¹⁷ and *never determined*
whether 1.0mg is “optimal” (despite contrary suggestions in their declarations).

PO Sur-Reply at 21

In re Fulton

391 F.3d 1195, 1200, 1201-02 (Fed. Cir. 2004)

“[O]ur case law does not require that a particular combination must be the preferred, or the most desirable, combination described in the prior art in order to provide motivation for the current invention. ...

Appellants’ argument is unpersuasive from a legal standpoint because it again relies on the mistaken premise that the prior art must teach that a particular combination is preferred, or ‘optimal,’ for the combination to be obvious.”

PO Misreads *SNF S.A. v. Solenis Techs.* Routine optimization does not require the claimed value is “optimum”

***SNF* does not say routine optimization requires a claimed optimum**

Second, to apply “routine optimization,” the claimed value must be “optimum.” *Id.* But Petitioner’s expert concedes: “I don’t think there’s any data to

POR at 49

terson, 315 F.3d 1325, 1330 (Fed. Cir. 2003). And *SNF S.A. v. Solenis Technologies, L.P.*, IPR2020-01730, Pap.10, 16-19 (Apr. 22, 2021) shows a claimed optimum is required: the Board analyzed whether optimizing would actually *lead to the claimed value*, not whether POSITA would *try* it. *Id.* Petitioner

PO Sur-Reply at 21-22

SNF S.A. v. Solenis Technologies, L.P.,
IPR2020-01730, Pap. 10 at 17 (PTAB Apr. 22, 2021)

“The record does not support that a POSA would have arrived at the claimed ratio using routine experimentation to optimize the ratio of WAMW to % DADMAC because, as Patent Owner explains, ‘there is no evidence that skilled artisans knew that the claimed ratio of WAMW to % DADMAC *was a parameter of any importance or one worth optimizing.*’ *Petitioner does not direct us to any teaching in the art recognizing the claimed ratio as having any import.*”
(emphasis added)

The '462 Patent Claims Are *Prima Facie* Obvious

**That shifts the production burden to PO
to show secondary considerations**

Galderma Laby's, L.P. v. Tolmar Inc.,
737 F.3d 731, 738 (Fed. Cir. 2013)

“In these circumstances, where there is a range disclosed in the prior art, and the claimed invention falls within that range, the burden of production falls upon the patentee to come forward with evidence that (1) the prior art taught away from the claimed invention; (2) there were new and unexpected results relative to the prior art; or (3) there are other pertinent secondary considerations.”

The Case for Obviousness

In response to *prima facie* obviousness, PO argues:

- Criticality of the 1.0 mg dose
- Secondary considerations
 - Commercial Success
 - Unexpected Results
 - Long-Felt Need
 - Industry Praise
 - Skepticism
- PO does not argue teaching away

**Secondary Considerations Cannot Overcome
Prima Facie Obviousness Here**

Secondary Considerations Principles

ZUP, LLC v. Nash Mfg., Inc.,
896 F.3d 1365, 1373 (Fed. Cir. 2018).

Patent Owner “bears the burden of production with respect to evidence of secondary considerations of nonobviousness.”

Perfect Web Techs., Inc. v. InfoUSA, Inc.,
587 F.3d 1324, 1333 (Fed. Cir. 2009).

Secondary considerations evidence, even if proven, does not always overcome a strong *prima facie* obviousness case.

The *prima facie* case is strong: assuming no anticipation, the only arguably missing limitation is a dose falling squarely in a narrow prior art range

No Nexus to the '462 Patent Claims

General Nexus Principles

Fox Factory, Inc. v. SRAM, LLC,
944 F.3d 1366, 1373 (Fed. Cir. 2019) (cleaned up)

“[E]vidence of secondary considerations must have a nexus to the claims, *i.e.*, there must be a legally and factually sufficient connection between the evidence and the patented invention.”

Merck & Cie v. Gnosis S.P.A.,
808 F.3d 829, 837 (Fed. Cir. 2015).

“Where objective indicia ‘result[] from something other than what is both claimed and *novel* in the claim, there is no nexus to the merits of the claimed invention.’ (citation omitted)

Nexus Principles: No Presumption of Nexus Absent Co-extensivity

Fox Factory, Inc. v. SRAM, LLC,
944 F.3d 1366, 1373, 1375 (Fed. Cir. 2019) (cleaned up)

“Whether a product is coextensive with the patented invention, and therefore whether a presumption of nexus is appropriate in a given case, is a question of fact. ... A patent claim is not coextensive with a product that includes a ‘critical’ unclaimed feature that is claimed by a different patent and that materially impacts the product’s functionality....”

Weight Loss Outcomes: No Nexus to the Claims

Weight loss is not an element of the '462 claims.

E.g., Ex. 1313 (18:3 – 19:12); Ex. 1310 (57:22-58:6).

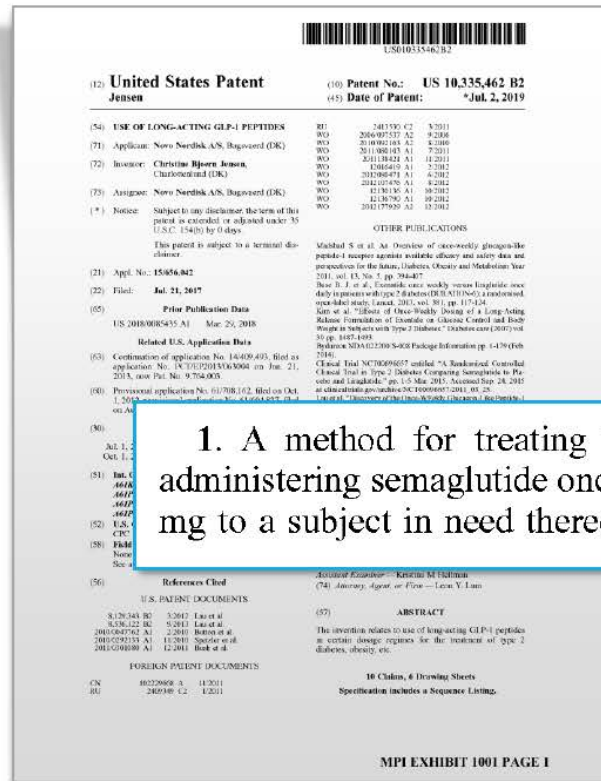
- PO has a different patent – U.S. Patent No. 9,764,003 – that claims “a method for reducing body weight” by “administering semaglutide once weekly in an amount of at least 0.7 mg and up to 1.6 mg to a subject in need thereof.”

Ex. 2002 (35:30-35).

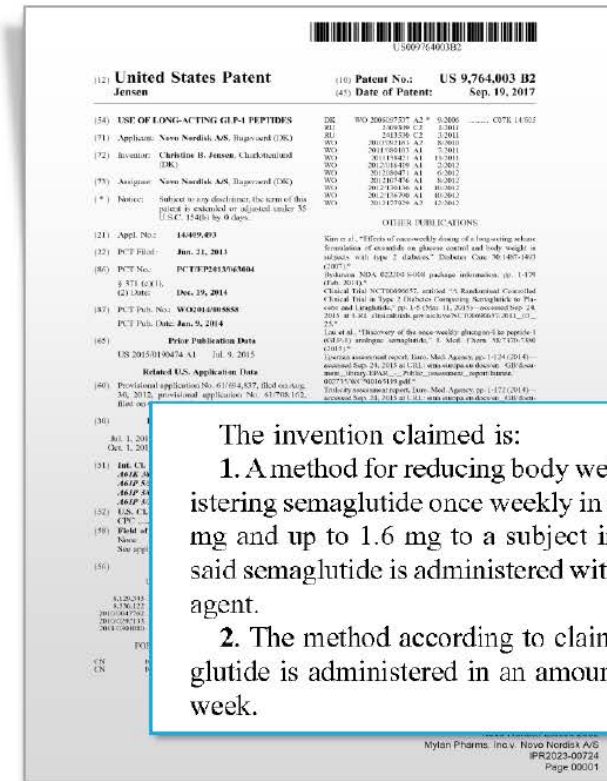
- PO's secondary considerations experts were unaware of it.

Ex. 1140 (15:7-13; 78:6-17); Ex. 1310 (57:22-58:13); Ex. 1314 (12:11-18).

Weight Loss Outcomes: No Nexus to the Claims



Ex. 1001 (35:42-44).



The invention claimed is:

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.
2. The method according to claim 1, wherein said semaglutide is administered in an amount of at least 0.8 mg per week.

Ex. 2002 (35:30-38).

The '003 patent claims a weight reduction method using a once-weekly 1.0mg semaglutide dose

Weight Loss Outcomes: No Nexus to the Claims

- PO's secondary considerations experts were unaware of the '003 patent.

Dr. Goland

Transcript of Robin S. Goland, M.D.
Conducted on April 9, 2024 78

1 which, in turn, reduces A1c.
2 Q And it's fair to say you discuss the
3 effect of semaglutide on body weight repeatedly
4 throughout your declaration; is that fair?
5 A Yes.

6 Q And I take it because you didn't
7 review any other patents in this case -- were
8 you unaware that Novo Nordisk has another
9 patent, what we call the '003 patent, that
10 claims the use of a once-weekly dose of
11 semaglutide, including a 1 milligram dose, for
12 reducing body weight in a subject in need
13 thereof?
14 A I don't --
15 MS. WU: Objection to form.
16 THE WITNESS: Oh, sorry.
17 A I'm not familiar with that patent.

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MPI EXHIBIT 1140 PAGE 78

Ex. 1140 (78:6-17).

Dr. Vellturo

CONFIDENTIAL - PROTECTIVE ORDER MATERIAL
Transcript of Christopher A. Vellturo, Ph.D.
Conducted on April 24, 2024 12

1 Do I don't know for the purposes of this 09:15:20
2 case. 09:15:22
3 Q So you don't have an opinion on whether 09:15:26
4 or not Ozempic is coextensive with the '343 patent? 09:15:28
5 MR. WU: Objection to form. 09:15:33

11 Q So you're getting your understanding that 09:15:58
12 Ozempic is coextensive with the '462 patent from 09:16:02
13 Dr. Goland. 09:16:04
14 Is that right? 09:16:05
15 A Yes. 09:16:05
16 Q And you don't have an independent opinion 09:16:06
17 on that aside from her understanding? 09:16:08
18 A I do not. 09:16:12

78 09:16:45
21 09:16:47
22 09:16:48

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PROTECTIVE ORDER MATERIAL MPI EXHIBIT 1314 PAGE 12

Ex. 1314 (12:11-18).

Dr. Bakris

Transcript of George Bakris, M.D.
Conducted on April 4, 2024 58

1 looked at earlier, that's not directed to a method 14:25:11
2 for treating people who are overweight or obese. 14:25:44
3 correct? 14:25:47
4 MR. MILEA: Objection, scope. 14:25:49
5 A Not sure. Based on the timing, I would 14:25:51
6 14:25:52

7 Q Okay. Were you aware that Novo Nordisk 14:25:59
8 has a separate patent, U.S. Patent Number 14:26:02
9 9,764,003, that claims a method for reducing body 14:26:09
10 weight by administering once-weekly semaglutide in 14:26:13
11 an amount that includes 1 milligram? 14:26:16
12 MR. MILEA: Objection, scope. 14:26:19
13 A I do not know. 14:26:21

18 14:26:33
19 14:26:43
20 14:26:43
21 14:26:44
22 14:26:51

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MPI EXHIBIT 1310 PAGE 58

Ex. 1310 (58:7-13).

Cardiovascular and Kidney Outcomes: No Nexus to the Claims

PO also relies on secondary considerations concerning “cardiovascular outcomes” and “kidney-protective effects.”

Ex. 2055, ¶ 33; Ex. 2011, ¶ 44.

- But those effects are the subject of the '032 patent application, claiming use of once-weekly semaglutide doses “of 0.05-2.0 mg” for “reducing the risk of a major adverse cardiovascular event” “wherein the subject has type 2 diabetes and cardiovascular disease.”

Ex. 1296 at 1, 11, 21-25 ('032 Appl. Claims and Response; Hvelplund Declaration); Ex. 1304, ¶¶ 127-130.

- Dependent claims in the '032 application also tie the subject’s “cardiovascular disease” to “chronic renal impairment.”

Ex. 1296 at 1 (Claim 17), 12-13, 24-25; Ex. 1306, ¶¶ 115-118.

Weight Loss, Cardiovascular, and Kidney Outcomes: No Presumption

Fox Factory, Inc. v. SRAM, LLC,
944 F.3d 1366, 1375-77 (Fed. Cir. 2019)

“Where a product embodies claims from two patents, a presumption of nexus can be appropriate only if the claims of both patents generally cover the same invention.”

'462

Method for treating T2D

'003

Method for reducing body weight

'032 App.

Method of reducing risk of major adverse cardiovascular event

**Do not
all generally
cover the
same invention**

Pet. Reply 35-36; Ex. 1302, ¶¶ 168-182, 228-230;
Ex. 1304, ¶¶ 127-130; Ex. 1306, ¶¶ 115-118

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

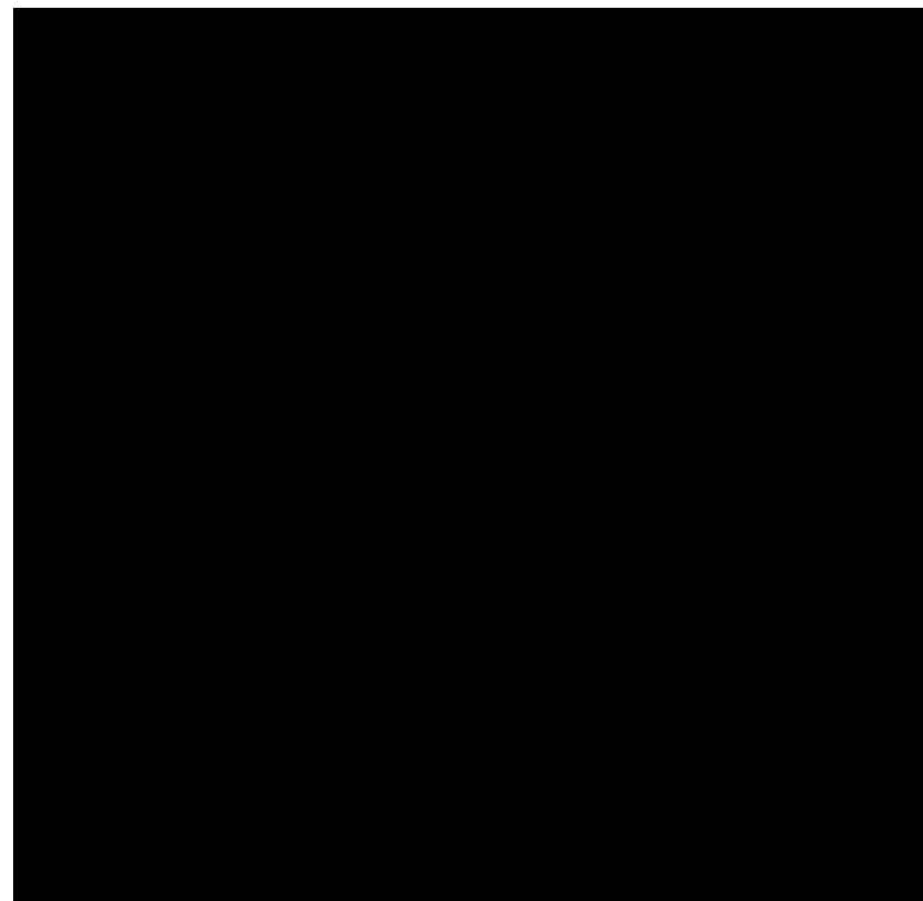
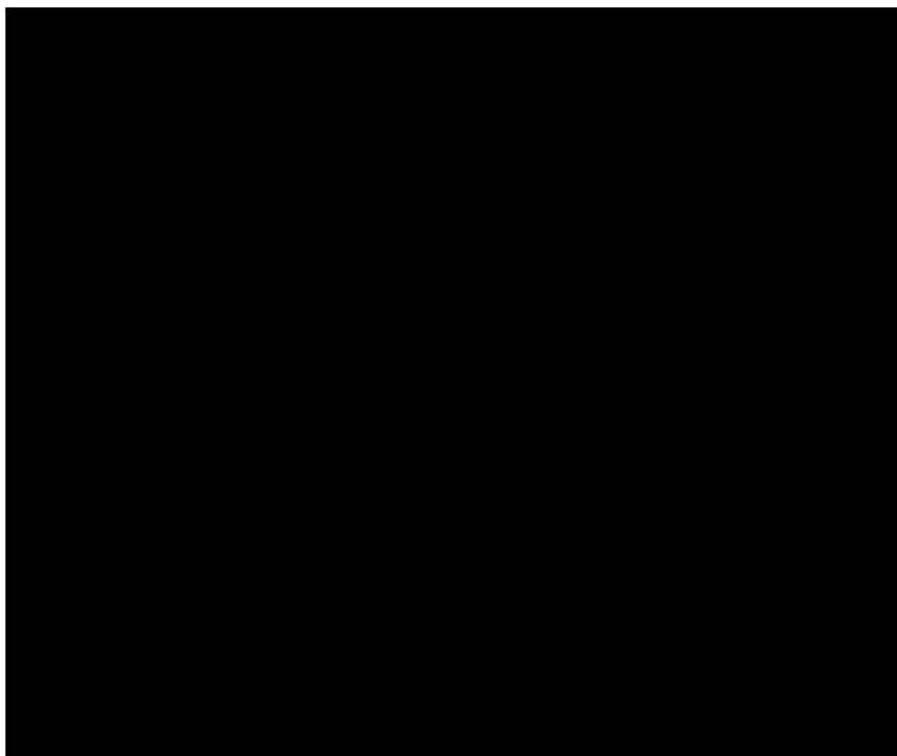
64

MPI EXHIBIT 1334 PAGE 64

PO Has Argued Weight Loss is Critical to Ozempic's Efficacy, Prescriptions, and Popularity

F.4th 1406, 1419 (Fed. Cir. 2022). Although important, these are not “features” that “materially impact[] the product’s functionality,” such that the nexus presumption shouldn’t apply. Rep.34-35; see *Fox Factory*, 944 F.3d at 1375.

PO Sur-Reply at 27-28.



PO Is Not Entitled to a Nexus Presumption

A nexus presumption cannot be founded on unclaimed features

features... as critical.” Cf. Rep.34-35. And evidence that “products embody the full scope of the claimed invention” supports a nexus presumption even when unclaimed features are present. *Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.*, 24 F.4th 1406, 1419 (Fed. Cir. 2022). Although important, these are not “features”

Quanergy Sys., Inc. v. Velodyne Lidar USA, Inc.,
24 F.4th 1406, 1418-19 (Fed. Cir. 2022)

“There is no dispute the Board must consider unclaimed features as part of its presumption analysis when they are raised.”

* * *

“Some unclaimed features ‘amount to nothing more than additional insignificant features,’ such that presuming nexus is still appropriate. Other unclaimed features, like ‘a critical unclaimed feature that is claimed by a different patent and that materially impacts the product’s functionality,’ indicate that the claim is not coextensive with the product.”

* * *

“Here, Quanergy, at best, presented only a skeletal, undeveloped argument to the Board.” (citations omitted)

No Relevant Commercial Success

PO Did Not Meet its Commercial Success Production Burden

Merck & Cie v. Gnosis S.P.A.,
808 F.3d 829, 837 (Fed. Cir. 2015) (citation omitted).

“If commercial success is due to an element in the prior art, no nexus exists.”

Galderma Lab’ys, L.P. v. Tolmar, Inc.,
737 F.3d 731, 740 (Fed. Cir. 2013) (citation omitted).

“However, if the feature that creates the commercial success was known in the prior art, the success is not pertinent.”

UCB, Inc. v. Actavis Lab’ys UT, Inc.,
65 F.4th 679, 696 (Fed. Cir. 2023)

“By contrast, [PO’s] expert ... did not analyze whether [PO’s] multiple patents were responsible for commercial success.”

PO's Purported Commercial Success Does Not Stem from What Is Claimed and *Novel*

- Using once-weekly subcutaneous semaglutide injections to treat T2D is indisputably in the prior art.

E.g., Ex. 1011; Ex. 1012; Ex. 1013; Ex. 1003, ¶¶ 136, 256, 298; Ex. 1300, ¶¶ 68-70, 74-77.

- U.S. Patent Nos. 8,129,343 and 8,536,122 claim the semaglutide molecule and its use to treat T2D.

Ex. 1068 (claims 1-6); Ex. 1067 (claims 1-2, 4-11, 15); Ex. 1302, ¶¶ 275-276.

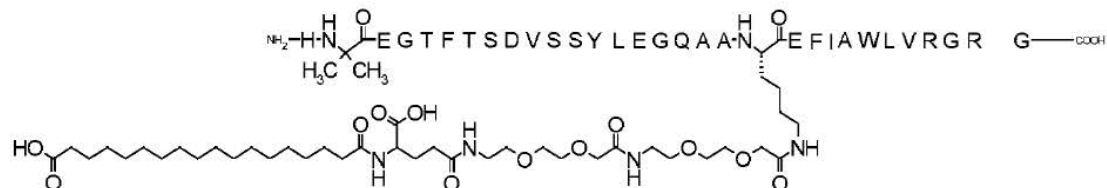
- Patent Owner contends 1.0 mg dose not in prior art, but weekly dosing and efficacy are due to semaglutide's molecular structure, not the 1.0mg dose.
 - Ex1302, ¶¶ 227, 289.
 - PO Literature: Ex. 2082 at 8; Ex. 2083 at 2; Ex. 1140 (53:1-55:19; 62:2-20; 73:4-10).
 - Approval at other doses (0.5 and 2.0 mg). Ex. 2076 at 3-4; Ex. 1140 (31:9-32:12, 34:2-5; 35:17-36:1) (explaining “Ozempic has multiple approved dosages, which allows me to tailor treatment to patients as their needs change over time”); Ex. 1302, ¶¶ 220-222; Ex. 1308, ¶¶ 36-44.

The '343 Patent Disclosed Once Weekly Semaglutide to Treat T2D

(12) United States Patent Lau et al.		(10) Patent No.: US 8,129,343 B2
		(45) Date of Patent: Mar. 6, 2012
(54) ACYLATED GLP-1 COMPOUNDS	WO	WO 00/34331 6/2002
	WO	WO 02/46227 6/2002
(75) Inventors: Jesper Lau , Farum (DK); Paw Bloch , Taastrup (DK); Thomas Kruse Hansen , Herlev (DK)	WO	WO 00/246227 6/2002
	WO	WO 02/098446 12/2002
	WO	WO 03/040309 5/2003
	WO	WO 2004/065621 8/2004
(73) Assignee: Novo Nordisk A/S , Bagsvaerd (DK)	WO	WO 2004/099246 11/2004
	WO	WO 2005/014049 2/2005
(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 682 days.	WO	WO 2005/027978 3/2005
	WO	WO 2005/027978 3/2005
	WO	WO 2006/097537 9/2006

Ex. 1068 at 1.

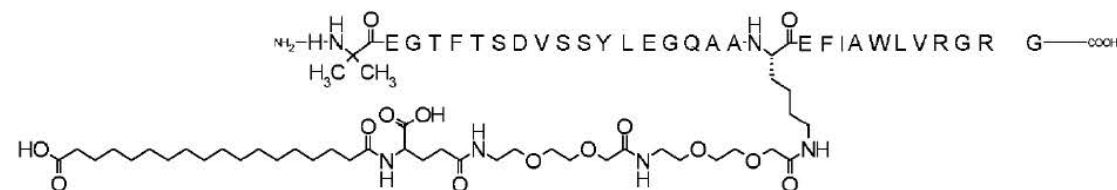
1. A compound of the structure



where the amino acid sequence is that of SEQ ID NO:7.

Ex. 1068, claims 1 (structure), 4 (chem. name).

3. A method for treating type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a pharmaceutical composition comprising a compound of the structure



where the amino acid sequence is that of SEQ ID NO:7, and a pharmaceutically acceptable excipient.

Ex. 1068, claims 3 (structure), 6 (chem. name).

PO's Purported Commercial Success Does Not Stem from What Is Claimed and Novel

Weekly dosing and efficacy are due to semaglutide's molecular structure, not the 1.0mg dose.

The SUSTAIN 10 trial showed that OW semaglutide 1.0 mg was superior to OD liraglutide 1.2 mg in reducing HbA_{1c} and body weight after 30 weeks of treatment in subjects with T2D uncontrolled on 1–3 OADs, few of whom received rescue medication. A greater proportion of subjects achieved HbA_{1c} targets of < 7.0% and ≤ 6.5% and weight-loss responses of ≥ 5% and ≥ 10% with semaglutide vs liraglutide. The observed differences in efficacy between the two medications could be due to minor but clinically relevant differences in their molecular structure: compared with liraglutide, which has an alanine at position 8 and a C-16 fatty acid chain with a gamma glutamate (γGlu) linker at position 26, semaglutide has an alanine to alpha-aminoisobutyric acid amino acid substitution at position 8 and a C-18 fatty diacid side chain with a γGlu-2xOEG linker at position 26 [30].

Semaglutide, a GLP-1 analogue currently in development, is structurally similar to liraglutide, an approved once-daily GLP-1 analogue. Structural modifications of the semaglutide molecule include aminoacid substitutions at position 8 (alanine to α-aminoisobutyric acid) and position 34 (lysine to arginine), and acylation of the lysine at position 26 with a spacer and C-18 fatty diacid chain.⁸ The substitution at position 8 renders semaglutide less susceptible to degradation by dipeptidyl peptidase-4 (DPP-4), and the lysine acylation improves binding to albumin.⁸ These modifications extend the half-life of semaglutide to roughly 1 week,⁸ enabling its once-weekly administration.^{9,10}

Ex. 2082 at 8.

Q But as we've seen today in some of the articles that you cite in your declaration, the ability to dose semaglutide once weekly is attributable to the half-life afforded by its chemical structure, correct?

MS. WU: Objection. Scope and form.

A Yes.

Ex. 1140 (73:4-10).

Ex. 2083 at 2.

No Commercial Success Nexus

- Dr. Vellturo relied on Dr. Goland for nexus

Ex. 1314 (12:3-18).

- Dr. Goland did not review any prior art to the '462 patent and did not know there were “earlier patents for semaglutide ... prior to [the '462] patent.”

Ex. 1140 (26:10-19; 11:3-6; 15:7-13; 18:1-19:18).

- See *UCB, Inc. v. Actavis Laby's UT*, 65 F.4th 679, 696 (Fed. Cir. 2023) (faulting expert for “not analyz[ing] whether UCB’s multiple patents were responsible for commercial success”); Ex. 1308, ¶¶ 29-35.

- PO also relied on tolerability and convenience

- Dr. Goland conceded tolerability is from an unclaimed dosing regimen.

Ex. 1140 (36:15-37:17); Ex. 1302, ¶ 219.

- Once-weekly dosing is in prior art and goes to the active ingredient, not 1.0mg dose.

Ex. 1308, ¶¶ 36-44; Ex. 1302, ¶ 289; Ex. 1140 (73:4-10).

No Commercial Success Nexus

Dr. Velturo relied on Dr. Goland for nexus

CONFIDENTIAL - PROTECTIVE ORDER MATERIAL Transcript of Christopher A. Velturo, Ph.D. Conducted on April 24, 2024		
	12	
1	So I don't know for the purposes of this	09:15:20
2	case.	09:15:22
3	Q So you don't have an opinion on whether	09:15:26
4	or not Ozempic is coextensive with the '343 patent?	09:15:28
5	MR. MAY: Objection to form.	09:15:33
6	A I don't have an opinion in this area at	09:15:34
7	all. These are understandings I received from	09:15:36
8	Dr. Goland and from counsel.	09:15:40
9	My understandings for the purposes of my	09:15:42
10	work here are what's memorialized in paragraph 83.	09:15:44
11	Q So you're getting your understanding that	09:15:58
12	Ozempic is coextensive with the '462 patent from	09:16:02
13	Dr. Goland.	09:16:04
14	Is that right?	09:16:05
15	A Yes.	09:16:05
16	Q And you don't have an independent opinion	09:16:06
17	on that aside from her understanding?	09:16:08
18	A I do not.	09:16:12
19	Q Okay. So some of the drivers of Ozempic	09:16:12
20	sales that you reference in your declaration are	09:16:45
21	tolerability.	09:16:47
22	Is that right?	09:16:48
PLANET DEPOS 888.433.3767 WWW.PLANETDEPOS.COM		
PROTECTIVE ORDER MATERIAL MPI EXHIBIT 1314 PAGE 12		

3	Q So you don't have an opinion on whether	09:15:26
4	or not Ozempic is coextensive with the '343 patent?	09:15:28
5	MR. MAY: Objection to form.	09:15:33
6	A I don't have an opinion in this area at	09:15:34
7	all. These are understandings I received from	09:15:36
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9	My understandings for the purposes of my	09:15:42
10	work here are what's memorialized in paragraph 83.	09:15:44
11	Q So you're getting your understanding that	09:15:58
12	Ozempic is coextensive with the '462 patent from	09:16:02
13	Dr. Goland.	09:16:04
14	Is that right?	09:16:05
15	A Yes.	09:16:05
16	Q And you don't have an independent opinion	09:16:06
17	on that aside from her understanding?	09:16:08
18	A I do not.	09:16:12

Ex. 1314 (12:3-18).

No Commercial Success Nexus

Dr. Goland did not review any prior art to the '462 patent and did not know there were “earlier patents for semaglutide ... prior to [the '462] patent.”

10 In reaching your opinions in this
11 case, did you consider whether the prior art to
12 the '462 patent disclosed the use of semaglutide
13 to treat type 2 diabetes?

14 MS. WU: Objection. Form.

15 A So you're asking were there earlier
16 patents for semaglutide, I would say, prior to
17 this patent?

18 Q Sure.

19 A I'm not aware that there were.

Ex. 1140 (26:10-19).

3 Q Aside from the '462 patent, did
4 review any other patents in preparing your
5 expert declaration?

6 A No, I did not.

Ex. 1140 (11:3-6).

7 Q And, as I understand it, in
8 determining whether there was a nexus between
9 things like unexpected results and other
10 objective indicia in the '462 patent claims, you
11 didn't look at any other patents that may or may
12 not cover Ozempic; is that fair to say?

13 A That is true.

Ex. 1140 (15:7-13).

14 Q Okay. The only references that you
15 list in your appendix are from after what we
16 call the priority date, so after July of 2012;
17 is that fair?

18 A That is correct.

Ex. 1140 (19:14-18).

No Commercial Success: Blocking Patents

Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.

97 F.4th 915, 935-36 (Fed. Cir. 2024) (cleaned up)

Blocking patents can “diminish[] possible rewards from a non-owner’s or non-licensee’s investment activity aimed at an invention whose commercial exploitation would be infringing,” leading to a “decrease in incentives [that] can discount the significance of evidence of commercial success and long-felt need.”

- Quintessential blocking patents: '343 and '122 patents claim semaglutide dosing and its use to treat T2D (applications filed 2006).

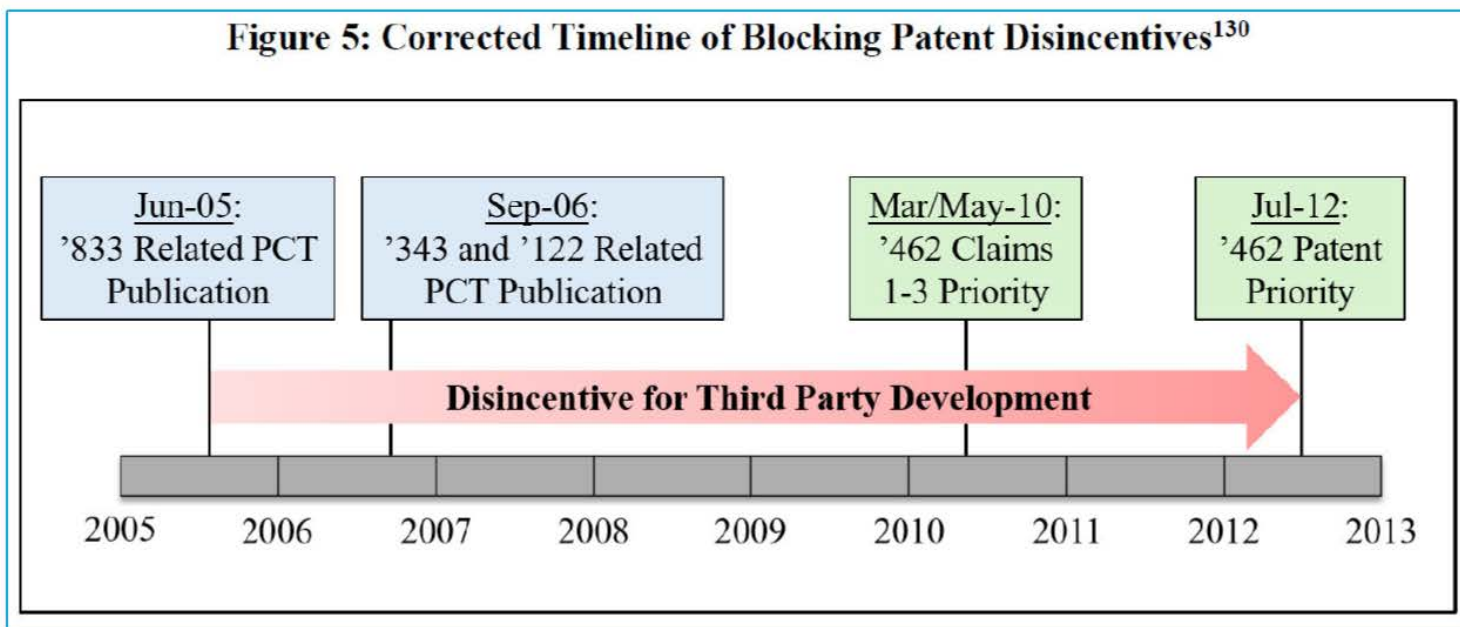
Ex. 1308, ¶¶ 71-85; Ex. 1302, ¶¶ 275-276.

Ex. 1209 at 1.

- Public knowledge of coverage would have disincentivized development of the claimed subject matter years before the priority date.

Ex. 1308, ¶¶ 76-84; Ex. 1302, ¶ 277.

No Commercial Success: Blocking Patents



Ex. 1308, ¶ 83.

No Commercial Success: Blocking Patents

- Blocking patents cover T2D treatment with semaglutide and would broadly block '462 patent claims
- Publicly known that PO was actively testing semaglutide in PI and PII clinical trials before the priority date
- No evidence Novo was willing to license patents covering Ozempic

Ex. 1308, ¶¶ 73-74, 76, 81, 85

PO's Dr. Vellturo agreed that published patent applications can have a blocking effect

Q And in offering that opinion, is it your view that for there to be a blocking issue, a patent needs to have issued?

A That's quite typically the case. But certainly, there can be matters of degree of publication. But -- so it's not an absolute clear line.

Q So can patent applications potentially present a blocking issue?

MR. MAY: Objection to form.

A I think that's too strong a statement. I think it's a matter of degree.

Is it possible that they can have some effect? I think it's possible.

Ex. 1314 (28:2-15).

No Unexpected Results

No Unexpected Results: Failure to Compare to Closest Prior Art

Janssen Pharms., Inc. v. Teva Pharms. USA, Inc.

97 F.4th 915, 933 (Fed. Cir. 2024)

“The starting reference point for evaluating unexpectedness is the closest prior art.”

- Closest prior art: 0.8 mg semaglutide dose identified in NCT657 (Ex. 1013) or the 1.8mg dose of the structurally-similar GLP-1 agonist liraglutide.

Ex. 1302, ¶¶ 205-208; Ex. 1002 at 344-45.

- PO comparators: insulin glargine, sulphonylureas, meglitinides, metformin, dulaglutide, exenatide ER, and the lower 1.2mg liraglutide dose.

POR 84; Ex. 2054, ¶¶ 61-74; Ex. 1140 (22:7-23:15; 25:1-26:8; 50:6-51:1; 65:20-66:16; 71:19-72:1);
Ex. 1310 (15:9-16:8); Ex. 1258 (12:5-17).

No Unexpected Results: Failure to Compare to Closest Prior Art

Dr. Goland did not review any prior art to the '462 patent and failed to measure alleged unexpected results against the closest prior art.

Q And I didn't see anything in your declaration where you identified what you view as the closest prior art to the '462 patent. If there is someplace in your declaration where you think you did that, could you point it out to me?

A I do not think those words are exactly in there.

Ex. 1140 (26:1-8).

Q Okay. Did you investigate whether there is any literature comparing HbA1c and weight reduction in type 2 diabetes patients of a 1.8 liraglutide dose to a 1 milligram semaglutide dose?

A No, I did not.

Ex. 1140 (50:6-11).

Q So, in other words, just so I understand your testimony, you would get greater HbA1c reduction and weight reduction with a 1.8 milligram dose of liraglutide than a 1.2 milligram dose of liraglutide?

A Yes.

Ex. 1140 (50:18 – 51:1).

Q Okay. The only references that you list in your appendix are from after what we call the priority date, so after July of 2012; is that fair?

A That is correct.

Ex. 1140 (19:14-18).

No Unexpected Results: Differences Merely of Degree

UCB, Inc. v. Actavis Lab'ys UT, Inc.,
65 F.4th 679, 696 (Fed. Cir. 2023)

“A difference of degree is not as persuasive as a difference in kind—i.e., if the range produces ‘a new property dissimilar to the known property,’ rather than producing a predictable result but to an unexpected extent. Furthermore, evidence of superior efficacy does not undercut a reasonable expectation of success.”

- No PO expert knew or considered this legal principle.

See Ex. 2011 (¶¶ 21-26) & Ex. 1310 (15:4-8); Ex. 2054 (¶¶ 19-26) & Ex. 1140 (12:19-13:1); Ex. 2055 (¶¶ 13-20) & Ex. 1258 (10:6-20).

- PO's experts conceded differences in degree.

Ex. 1140 (51:10-20 (HbA1c and weight reduction differences are ones of degree vs prior art));
Ex. 1258 (74:16-75:1 (compared to “other therapies” semaglutide showed a greater cardiovascular “degree of benefit”)).

- Petitioner's experts established differences are only of degree, not kind.

Ex. 1302, ¶¶ 252-257; Ex. 1304, ¶¶ 135-140, 150-159; Ex. 1306, ¶¶ 139-144.

No Unexpected Results: Differences Merely of Degree

PO's experts conceded differences in degree.

Q All right. And SUSTAIN 10 found that the participants administered both semaglutide and liraglutide achieved reductions in HbA1c and weight; is that right?

A Yes.

Q And your opinion is that it is the patients in the semaglutide trial arm -- they saw their HbA1c and weight reduced to a greater degree than did the patients on liraglutide 1.2 milligrams; is that right?

A Yes.

Ex. 1140 (51:10-20).

Q And were those SUSTAIN-6 data surprising in view of the results for Bydureon?

MR. WHITE: Objection.

A Yeah. Yeah. Absolutely. It's absolutely, you know, super exciting and unexpected compared to other therapies that didn't show the same benefit -- degree of benefit or benefit on cardiovascular outcomes. So absolutely.

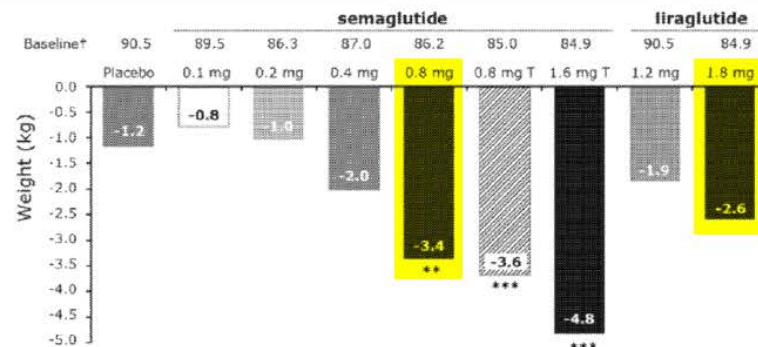
Ex. 1258 (74:16 – 75:1).

No Unexpected Results: Differences Merely of Degree

PO's attorney argument is not a substitute for expert analysis

ference in kind" is a "fact-specific" inquiry. *Id.* PO's experts and other evidence confirm the differences resulting from '462's claimed dose were differences in kind. *E.g.*, POR.83-87; EX2054, ¶¶61-83; EX2055, ¶¶34-44; EX2011, ¶¶44-63; EX1001, Fig.5 (30.8% greater weight loss in 0.8mg semaglutide (3.4kg) than 1.8mg liraglutide (2.6kg)); EX2082, 1, 6-7 (comparing 1.0mg semaglutide/1.2mg liraglutide at week 30, 211% more patients hit 5% weight loss (56%/18%), 375% more patients hit 10% weight loss (19%/4%), 205% greater average weight loss (5.8kg/1.9kg), and 70% greater reduction in HbA1c for semaglutide (1.7/1.0)).

PO Sur-Reply
at 34.



Ex. 1001, Fig. 5.

²¹ Petitioner's suggestion PO failed to compare 1.8 mg liraglutide is facially incorrect. POR.33, 84-85, 88. For example, PO's unexpected kidney results evidence for 1.0mg once-weekly semaglutide in T2D patients was compared against 0.5mg once-weekly semaglutide and 1.8mg daily liraglutide. *See* EX2015, 8; POR.85.

PO Sur-Reply at 32-33 n.21.

Effect of the Glucagon-Like Peptide-1 Receptor Agonists Semaglutide and Liraglutide on Kidney Outcomes in Patients With Type 2 Diabetes: Pooled Analysis of SUSTAIN 6 and LEADER

* * *

What Are the Clinical Implications?

- The results of this study suggest that the glucagon-like peptide-1 receptor agonists semaglutide and liraglutide may add to the kidney-protective treatment options available to people with type 2 diabetes and diabetic kidney disease.

Ex. 2015 at 1-2; *see also* Ex. 1306, ¶¶ 105, 131-132.

No Unexpected Results: Differences Merely of Degree

PO's experts failed to distinguish differences in degree and kind; Petitioner's experts did

ference in kind" is a "fact-specific" inquiry. *Id.* PO's experts and other evidence confirm the differences resulting from '462's claimed dose were differences in kind. *E.g.*, POR.83-87; EX2054, ¶¶61-83; EX2055, ¶¶34-44; EX2011, ¶¶44-63; EX1001, Fig.5 (30.8% greater weight loss in 0.8mg semaglutide (3.4kg) than 1.8mg liraglutide (2.6kg)); EX2082, 1, 6-7 (comparing 1.0mg semaglutide/1.2mg liraglutide at week 30, 211% more patients hit 5% weight loss (56%/18%), 375% more patients hit 10% weight loss (19%/4%), 205% greater average weight loss (5.8kg/1.9kg), and 70% greater reduction in HbA1c for semaglutide (1.7/1.0)).

PO Sur-Reply at 34.

38. The 26% reduction in three-point MACE with once-weekly subcutaneous semaglutide was particularly notable as compared to another GLP-1 receptor agonist, liraglutide, as studied in the LEADER trial (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results). Comparisons of these trials showed that a daily injection of liraglutide at 1.8mg demonstrated a 13% reduction in three-point MACE—only half of the 26% shown with once-weekly subcutaneous semaglutide. *See, e.g.*, EX2110 (Verges) at 2. Notably, semaglutide as evaluated in the SUSTAIN-6 trial showed a much greater reduction in nonfatal stroke, which is a finding that appears more robust (and clinically relevant) for semaglutide than any other therapy in the field. *See id.*

Ex. 2055 (Blaha), ¶ 38.

135. I understand that for unexpected results to be persuasive, the results produced by the claimed invention must be different in kind, and not merely in degree, from the results produced by the prior art. I understand that a difference in kind can be the presence of a new property dissimilar to the known property from the prior art. Dr. Blaha failed to demonstrate that the cardiovascular results associated with Ozempic® were of a different kind than those associated with the closest prior art, other GLP-1 receptor agonists, and other treatments for T2D.

* * *

137. Second, even considering the comparisons to liraglutide, semaglutide achieved similar kinds of results that liraglutide achieved, namely, a reduction in 3-point MACE. *See* EX2087 (ADA-2022) at Table 10.3B. Indeed, the ADA described the results of LEADER as "*consistent*" with the results from SUSTAIN-6. EX2087 (ADA-2022) at 22 ("Results from a moderate-sized trial of another GLP-1 receptor agonist, semaglutide, were consistent with the LEADER trial (194) [SUSTAIN-6]).").

Ex. 1304 (Schwartzbard), ¶¶ 135, 137.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

No Long-Felt Need

No Long-Felt but Unmet Need

PO argues: Ozempic® satisfied a long-felt need for a “safe, effective, and tolerable once-weekly T2D treatment” with significant weight loss.

POR at 87-88.

- Ozempic® was not the first safe, effective, and tolerable once-weekly GLP-1 agonist
Ex. 1302, ¶ 286; Ex. 1310 (70:12-17).
- Claims require no particular efficacy level
Ex. 1302, ¶ 285.
- Ozempic®’s tolerability results from an unclaimed titration regimen
Ex. 1302, ¶ 219.
- Once-weekly semaglutide is in the prior art, attributable to molecule
Pet. Reply 36-37.
- Weight gain argument based on *non*-GLP-1 medications. GLP-1 medications as a class were known to reduce weight.
Ex. 1302, ¶¶ 135-140; Ex. 1140 (72:7-18).
- Blocking patents undercut long-felt need.
Pet. Reply 38-39; *Janssen*, 97 F.4th at 935-36.

No Relevant Industry Praise or Skepticism

No Industry Praise or Skepticism

- Journal articles describe trials sponsored and paid for by PO and come from PO's employees.

Ex. 2082 at 1, 9; Ex. 2083 at 1; Ex. 2084 at 1; Ex. 2085 at 1, 8; *Bayer*, 713 F.3d at 1377 (rejecting patentee's "self-referential" "published efficacy studies" as evidence of praise).

- *New Yorker* and *New York Times* articles don't mention the 1.0 mg dose, and discuss obesity, weight loss, and potential uses of GLP-1 agonists other than treating T2D.

Ex. 2080; Ex. 2081; Ex. 1302, ¶¶ 291-306.

- Medical guidelines regarding cardiovascular risk recommend using any GLP-1 agonist, including liraglutide, dulaglutide, and semaglutide, or an SGLT-1 inhibitor.

Ex. 1304, ¶¶ 150-159.

- The only "industry skepticism" is Dr. Goland's choice to delay prescribing Ozempic® for a few months "until post-marketing reports and data were available."

POR 90 (citing Ex. 2054, ¶¶ 88-92); her colleagues used Ozempic® immediately upon approval. Ex. 1140 (98:19-100:6).

No Industry Praise or Skepticism

- *New Yorker* and *New York Times* articles, don't mention the 1.0 mg dose, and discuss obesity, weight loss, and potential uses of GLP-1 agonists other than treating T2D.

THE YEAR OF OZEMPIC

We may look back on new weight-loss drugs as some of the greatest advances in the annals of chronic disease.

every day, so it developed a once-weekly formulation. For reasons that remain a mystery, semaglutide, which is sold under the brand names Ozempic and Wegovy, caused profound reductions in weight. A two-hundred-pound woman might easily lose thirty pounds on the medication. People who had struggled to lose weight since childhood suddenly could.

including pills, which patients prefer to injections. In June, a clinical trial sponsored by Eli Lilly found that a pill with the melodious name orforglipron caused weight reductions on par with Ozempic's. Soon, millions of people could

It is hard to overstate how little progress the United States has made on this issue. Weight is not always a health problem: people with larger bodies can be metabolically healthy, just as people with normal B.M.I.s can develop diabetes and heart disease. But, over the years, obesity has been medicalized because of its links to diabetes, hypertension, and heartburn; arthritis, strokes, and heart disease; cirrhosis, sleep apnea, and kidney failure; depression, infertility, and cancer. Even so, the share of the population that is overweight has increased virtually every year since the nineteen-seventies. In the years after the National Institutes of Health essentially declared war on obesity, in 1998, rates of severe obesity doubled, and deaths from obesity-related heart disease tripled.

(Technically, Ozempic and Mounjaro are approved for diabetes, while Wegovy and Zepbound are approved for obesity. In practice, all have been used for weight loss, and "Ozempic"—which was the first to market—has become a kind of shorthand for the class.) Suspected fake Ozempic pens have spread across Europe

Ex. 2080.

No Industry Praise or Skepticism

- *New Yorker* and *New York Times* articles, don't mention the 1.0 mg dose, and discuss obesity, weight loss, and potential uses of GLP-1 agonists other than treating T2D.

Much of the research on other uses of semaglutide, the compound in Ozempic and Wegovy, and tirzepatide, the substance in Mounjaro and Zepbound, is only in the early stages. One of the biggest questions scientists are seeking to answer: **Do the benefits of these drugs just boil down to weight loss?** Or do they have other

Ozempic and other drugs like it have proven powerful at regulating blood sugar and driving weight loss. Now, scientists are exploring whether they might be just as transformative in treating a wide range of other conditions, from addiction and liver disease to a common cause of infertility.

Ex. 2081.

People with the conditions below, many of whom have few good options for treatment, could benefit in the long run if these trials are successful. **And for weight-loss drugmakers,** every new use could catapult the drugs even further into blockbuster status. Some of these applications — including for heart disease and sleep apnea, which each affects tens of millions of people — have become

Alcohol use disorder

Polycystic ovary syndrome

Cardiovascular issues

Kidney disease

Sleep apnea

Liver disease

No Industry Praise or Skepticism

- The only “industry” skepticism is Dr. Goland’s personal choice to delay prescribing Ozempic® for a few months until post-marketing data were available.

41. Ozempic® was first approved for clinical use in December 2017. Following Ozempic®’s approval I waited for several months of post-marketing data to begin to using it in my patients and first prescribed Ozempic® in the Spring of 2018.

Ex. 2054, ¶ 41.

Q Do you remember when in 2018 you first prescribed Ozempic?

A Not precisely.

Ex. 1140 (99:15-17).

Q You also say that you started to use Ozempic only after your colleagues used Ozempic and reported their positive experiences to you, correct?

A Yes.

Q So those colleagues, at least, must not have shared their skepticism since they started using it right after it was approved; is that fair?

A That is correct. There are the early adopters and the late adopters.

Ex. 1140 (99:18 – 100:6).

PO's Clinical Trial "Failure" Argument Is Wrong and Irrelevant

PO Has No Evidence the “Vast Majority” of Phase 2 Trials “Fail”

PO mischaracterizes the Arrowsmith “study”

The 1-page Arrowsmith article:

- Does not define “failure”
- Includes “failures” for “strategic reasons”
- Includes “failures” where no reason was reported
- Includes as “failures” trials ended “due to inadequate differentiation from more advanced drugs”
- Does not identify the studies or drugs on which its analysis is based

Arrowsmith’s Conclusion

Phase II failures: 2008–2010

* * *

Although it is difficult to draw conclusions from these data, the finding that a substantial proportion of Phase II failures were due to strategic reasons suggests that one important underlying factor could be overlapping R&D activity between companies with drugs in Phase II trials. This raises the question of whether an increase in collaborative efforts between companies up to the point of proof-of-concept for novel targets or mechanisms might be more cost- and time-effective.

Ex. 2006.

PO says POSAs Would Assume Phase 2 NCT657 Semaglutide T2D Dose-Finding Study Failed, but PO Announced It *Succeeded* Before the Priority Date

POR: POSA would assume NCT657 PII trial failed

To begin, it was entirely possible *none* of the tested dosages would be safe, effective, and tolerable and POSITA would need to try additional dosages outside the tested range based on body weight, different frequencies, etc.—or abandon semaglutide altogether.³² EX2010, ¶341; EX2018, 23:13-19 (Phase II “dose-

POR at 57.

dosing in treating diabetes. EX2010, ¶¶300-302; cf. Pet.39-40. POSITA would have been aware drugs undergoing expensive trials *often do not meet the endpoints due to safety, efficacy, and/or tolerability issues*. EX2006, 1; EX2010, ¶¶119-122,

POR at 44.

(d) Petitioner Ignores That The Phase III Semaglutide Study Was “On Hold”

* * *

inferences from the “on hold” status. EX1035, Table 1; EX2065, 26. Without additional information, POSITA would have concluded the hold was due to unfavorable trial outcomes (which were not publicly available) and been pointed to other listed GLP-1 analogues until more was known. EX2010, ¶¶376-379.

POR at 67-69.

PO to SEC and Public: NCT657 trial showed semaglutide efficacy, safety and tolerability broadly in line with liraglutide

Novo Nordisk May 1, 2009 Securities & Exchange Commission Form 6-K filing

Novo Nordisk very recently finalised a phase 2 study investigating safety and efficacy of five doses of semaglutide (NN9535), a once-weekly human GLP-1 analogue, versus placebo and open-label liraglutide add-on therapy in people with type 2 diabetes. At study start, patients were treated with metformin or controlled with diet and exercise. The 12-week multi-centre, multinational, double-blind, placebo-controlled, randomised dose-finding trial, which included a little more than 400 patients, demonstrated that clinical efficacy and safety of semaglutide was broadly in line with liraglutide. Semaglutide was generally well tolerated and was not associated with an increase in injection site reactions, antibody formation or calcitonin levels. After more detailed analysis of the dose-response findings on efficacy and safety, Novo Nordisk will discuss the future plans for semaglutide development with regulatory authorities before initiation of phase 3 development.

Ex. 1282 at 12.

Novo Nordisk Feb. 2, 2011 Securities & Exchange Commission Form 6-K filing

Once-weekly GLP-1 portfolio decision now expected mid-2012
As previously communicated in June 2010, Novo Nordisk has an intent to select among the two primary once-weekly GLP-1 candidates in the development portfolio, semaglutide and once-weekly liraglutide. To allow for a more complete characterisation of once-weekly liraglutide, including data from a clinical multiple-dose study, this decision is now expected mid-2012.

Ex. 1131 at 16.

Sanofi v. Watson Is Not a Range Case and Does Not Undermine REOS Here

POR at 59-60, discussing *Sanofi v. Watson Lab 'ys Inc.*, 875 F.3d 636 (Fed. Cir. 2017).

“In *Sanofi*, the Federal Circuit affirmed no REOS where the art disclosed ‘the rationale and design of the ... study’ testing the drug at issue in the relevant population and included a statement that ‘it is expected that treatment’ would work (as claimed in the asserted patent). ... **Rejecting this far more robust [REOS] showing than Petitioner offers here**, the Federal Circuit found 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.”

What PO Leaves Out: *Sanofi v. Watson Lab 'ys Inc.*, 875 F.3d 636, 641, 648 (Fed. Cir. 2017).

“As was explained in publications before [the priority date], the results of the ANDROMEDA trial, as they came in, led Sanofi to terminate the study early: **it appeared that dronedarone was actually increasing mortality from heart failure.**”

“Meanwhile, the ANDROMEDA study showed **dangers of dronedarone severe enough to have spurred early termination of the study.** A 2006 **European Medicines Agency** report doubted the presence of clinical benefits and **deemed the efficacy/safety ratio to be ‘negative.’** A 2007 article characterized the **safety and efficacy data as confusing and severely challenged.**”

Dependent Claim Limitations: Claims 4-10

The '424 Publication (Ex. 1016): Claims 4-10

The '424 Publication Disclosed Elements of Claims 4-10

Claim 4

- Claim 4: “an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.”

Ex. 1001 (35:49-52).

- The '424 publication disclosed formulating peptides in isotonic aqueous solutions with a phosphate buffer as a preferred formulation and with a pH between 7.0 and 9.0.

Ex. 1007, ¶¶ 191-196; Ex. 1016, [0003], [0180]-[0251].

- Examples 2-5 disclosed formulations with a phosphate buffer, a pH between 7.4 and 8.15, and isotonicity agents.

Ex. 1016, [0180]-[0251]; *see also* Ex. 1007, ¶¶ 147-196.

- POSAs understood human physiological pH is around 7.4, making it desirable to administer subcutaneous injections near that pH to avoid adverse reactions.

Ex. 1007, ¶¶ 194-195.

The '424 Publication Disclosed Elements of Claims 4-10

Claims 5 and 7

- Claims 5 and 7: administering semaglutide in a formulation that “comprises propylene glycol and phenol.”

Ex. 1001 (35:53-54, 36:42-43).

- The '424 publication taught propylene glycol and phenol would have stabilized the peptide formulation and they were both preferred excipients.

Ex. 1007, ¶¶ 199, 207; Ex. 1016, [0180]-[0251].

The '424 Publication Disclosed Elements of Claims 4-10

Claims 6 and 10

- Claims 6 and 10: Administering semaglutide at a pH of 7.4.

Ex. 1001 (36:40-41, 52-53).

- The '424 publication disclosed that formulations with a pH between 7.0 and 9.0, including specific formulations at pH 7.4, would minimize tissue damage and injection pain.

Ex. 1007, ¶¶ 203, 222; Ex. 1016, [0180]-[0251].

- POSAs understood human physiological pH is around 7.4, making it desirable to administer subcutaneous injections near that pH to avoid adverse reactions.

Ex. 1007, ¶¶ 173, 194, 201, 216, 220.

The '424 Publication Disclosed Elements of Claims 4-10

Claim 8

- Claim 8: “the phosphate buffer is a sodium dihydrogen phosphate buffer.”
Ex. 1001 (36:44-45).
- The '424 publication disclosed using sodium dihydrogen phosphate buffer in peptide formulations and identified it as “preferred.”
Ex. 1007, ¶ 211; Ex. 1016, [0180]-[0251].

The '424 Publication Disclosed Elements of Claims 4-10

Claim 9

- Claim 9: “subcutaneous injection in the form of an isotonic aqueous solution comprising at [sic] a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.”

Ex. 1001 (36:46-51).

- This claim is obvious for the same reason as claim 4.

Ex. 1007, ¶¶ 191-196, 213-219.

- The '424 publication also taught propylene glycol and phenol would have stabilized the peptide formulation, and they were both preferred excipients, making it obvious to use these excipients in the formulation.

Ex. 1007, ¶ 218; Ex. 1016, [0180]-[0251].

WO537 (Ex. 1015): Claims 4-10

WO537 Disclosed Elements of Claims 4-10

Claim 4

- Claim 4: “an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.”

Ex. 1001 (35:49-52).

- WO537 taught formulating isotonic aqueous peptide solutions using a phosphate buffer, isotonicity agents, and with a pH in the claimed range.

Ex. 1007, ¶¶ 254-259; Ex. 1015 (25:11-26:2, 26:4-8).

WO537 Disclosed Elements of Claims 4-10

Claims 5 and 7

- Claims 5 and 7: administering semaglutide in a formulation that “comprises propylene glycol and phenol.”

Ex. 1001 (35:53-54, 36:42-43).

- A POSA would have been motivated to administer semaglutide as a formulation that “comprises propylene glycol and phenol” and would have had a reasonable expectation in doing so.

Ex. 1007, ¶¶ 225-53.

- WO537 taught that propylene glycol and phenol would stabilize the formulation.

Ex. 1007, ¶¶ 262, 270; Ex. 1015 (26:11-35, 64:10-15).

WO537 Disclosed Elements of Claims 4-10

Claims 6 and 10

- Claims 6 and 10: Administering semaglutide at a pH of 7.4.

Ex. 1001 (36:40-41, 52-53).

- A POSA would have been motivated to administer semaglutide as a formulation with a pH of 7.4 and would have had a reasonable expectation in doing so.

Ex. 1007, ¶¶ 225-253.

- WO537 taught formulations with a pH between 7.0 and 9.0.

Ex. 1007, ¶¶ 264-267, 283-86; Ex. 1015 (25:11-26:2, 26:4-8).

- POSAs also knew the physiological pH was around 7.4.

Ex. 1007, ¶¶ 257, 264-67, 279, 283-86.

WO537 Disclosed Elements of Claims 4-10

Claim 8

- Claim 8: “the phosphate buffer is a sodium dihydrogen phosphate buffer.”

Ex. 1001 (36:44-45).

- A POSA would have been motivated to administer semaglutide in a formulation wherein “the phosphate buffer is a sodium dihydrogen phosphate buffer” and would have had a reasonable expectation in doing so.

Ex. 1007, ¶¶ 225-253, 272-275.

- WO537 disclosed the use of a sodium dihydrogen phosphate buffer as an “exemplary” buffer.

Ex. 1007, ¶¶ 272-275; Ex. 1015 (26:6).

WO537 Disclosed Elements of Claims 4-10

Claim 9

- Claim 9: “subcutaneous injection in the form of an isotonic aqueous solution comprising at [sic] a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.”

Ex. 1001 (36:46-51).

- A POSA would have been motivated to administer semaglutide as a “subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol” and would have had a reasonable expectation in doing so.

Ex. 1007, ¶¶ 225-253, 276-282.

- WO537 disclosed formulating GLP-1 agonists in isotonic aqueous solution with a sodium dihydrogen phosphate buffer as an “exemplary” buffer and with a pH between 7.0 and 9.0.

Ex. 1007, ¶¶ 279-281; Ex. 1015 (25:11-26:2, 26:4-8).

- WO537 also taught that propylene glycol and phenol stabilized the formulation.

Ex. 1007, ¶ 281; Ex. 1015 (26:11-35, 64:10-15).

No Basis for Additional Discovery or Sanctions

Mylan's *Sand Revolution* Stipulation

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN P

NO

Cas

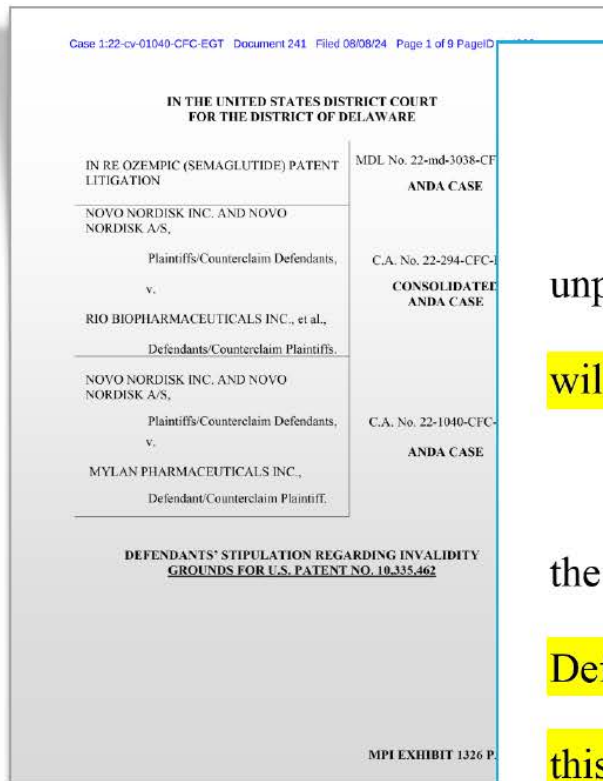
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PETITION FOR
U.S. P

Mylan: “[I]f the Board institutes, Petitioner will not pursue in the district court any instituted grounds against the originally-issued claims *unless a change in law otherwise permits.*”

Pet. at 66 (emphasis added).

Defendants' August 8 Stipulation



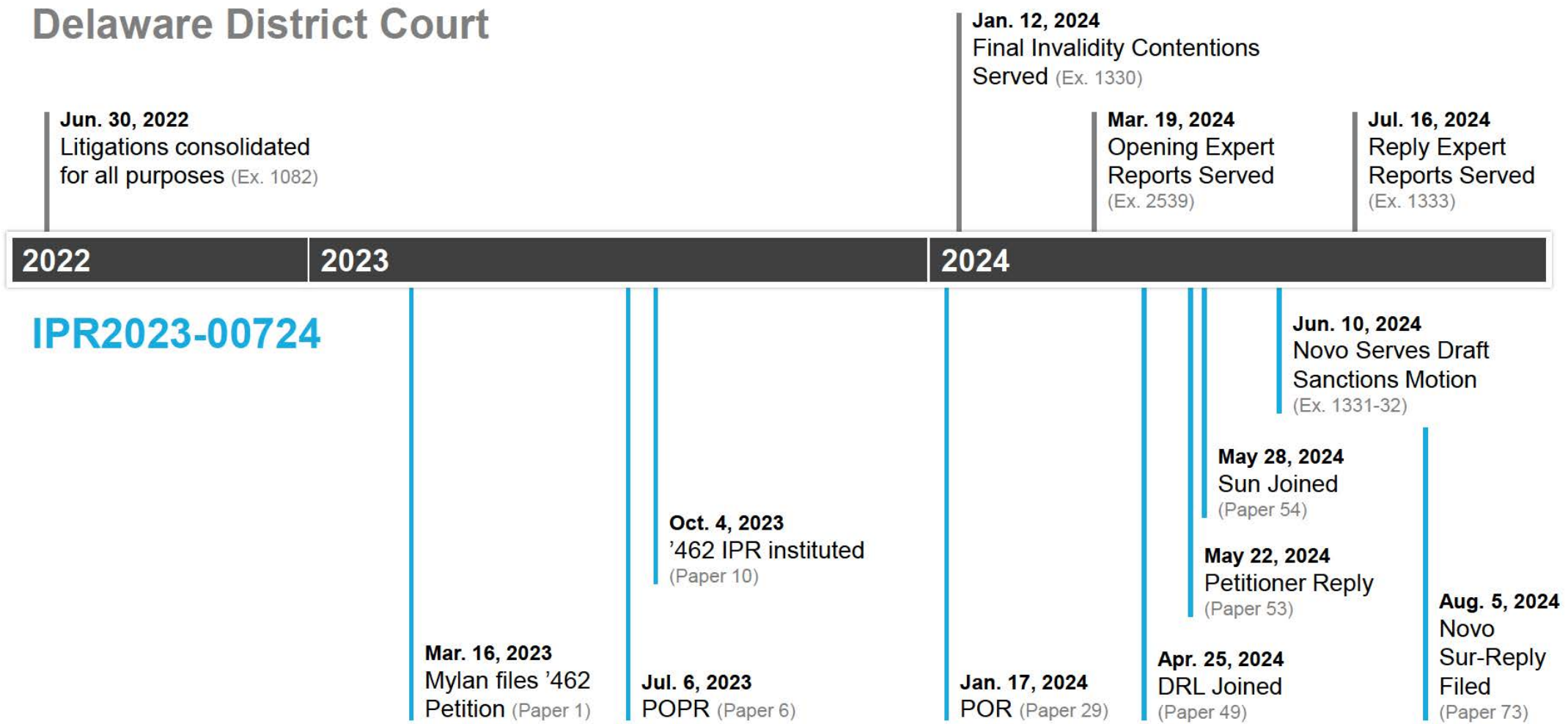
NOW THEREFORE, Defendants⁸ hereby stipulate and agree as follows:⁹

1. Because the PTAB will determine whether the '462 patent is unpatentable as anticipated or obvious with respect to the IPR Grounds, Defendants will not raise those same invalidity grounds at trial in this action;¹⁰
2. To the extent any of Defendants' experts in this action have opined that the '462 patent is invalid as anticipated or obvious on the basis of the IPR Grounds, Defendants agree those experts will not testify on those invalidity grounds at trial in this action;

Ex. 1326 at 5.

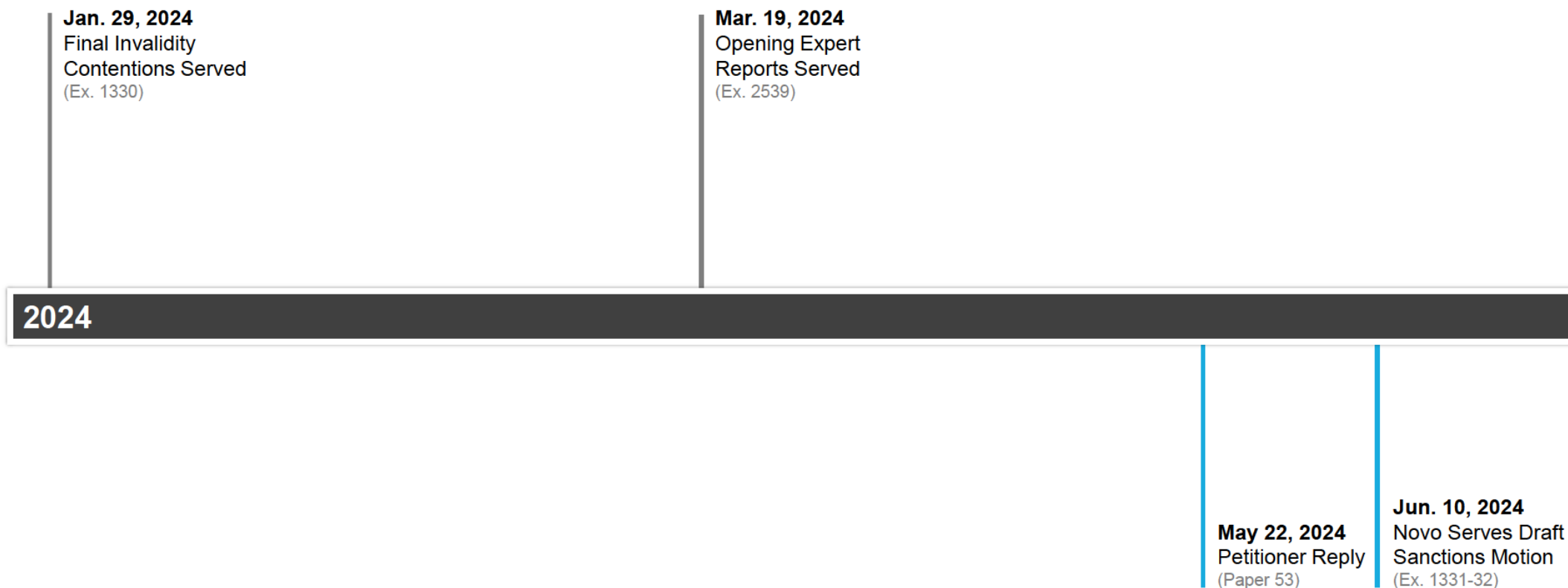
Timeline: District Court vs. IPR

Delaware District Court



IPR2023-00724

Novo's Delay Timeline



PO's Citation 1: REOS Arguments

255. A skilled artisan would also have known from Lovshin that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg semaglutide. Ex. 1012 (Lovshin) at 2, Table 1. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. See Ex. 1047 (Tamimi) at 3-4; Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6; Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

252. Skilled artisans would have known that Novo Nordisk was investigating a dose range of between 0.1-1.6 mg semaglutide once weekly to treat type 2 diabetes. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide.

253. To begin, skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance. Lund (Ex. 1035) at 5. As I

Ex. 1005,
¶¶ 252, 253, 255.

340. A skilled artisan would also have known from Lovshin 2009 that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg semaglutide. Lovshin 2009 at 263, Table 1. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. See Tamimi at ¶127-28; FDA Exposure Response 2003 at 4; ICH 1994 at 55972-74, 55976; Shargel at 577-78, Figs. 19-1 and 19-2.

341. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide. Skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance. Lund at 611.

342. In my opinion, by routine testing of the disclosed range of doses of semaglutide, a POSA would have been motivated with a reasonable expectation of success to use a weekly dose of 1.0 mg semaglutide by subcutaneous injection to treat type 2 diabetes. The '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious to achieve using routine experimentation:

Ex. 2551,
¶¶ 340-42.

PO's Citation 2: "Added" Data

262. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 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. *See, e.g.*, Ex. 1039 (Victoza label) at 2

97. NCT657 had six Experimental arms (A-F), which included once weekly subcutaneous (s.c.) injections of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration) semaglutide. *Id.* at 15-16. NCT657 also had six Placebo Comparator arms (G1-G6), which included once weekly subcutaneous injections of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration) placebo and two Experimental arms (H and I), which included once daily subcutaneous injections of 1.2 mg and 1.8 mg liraglutide, respectively. *Id.* at 16.

124. NCT657 had six experimental arms in the clinical trial (A-F), which included subcutaneous injections of semaglutide, once weekly, at doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration). *Id.* at 15-16. Skilled artisans would have understood that "with titration" meant that the recited dose amount was reached by starting from a lower dose amount and then increasing the dose until reaching the final level.

259. In particular, a skilled artisan would have been aware that the completed NCT657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. Ex. 1013 (NCT657) at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides further confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose of semaglutide and would have had a reasonable expectation of success in doing so.

Ex. 1005, ¶¶ 97,
124, 259, 262.

350. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. That the 0.8 mg dose was tested in NCT00696657 with and without titration and the 1.6 mg dose was tested only with titration would have suggested to skilled artisans that Novo Nordisk had reservations about the tolerability of the 1.6 mg dose considering it was only being tested with titration, whereas, the 0.8 mg dose was being tested with and without titration, which suggests that this dose would have a better balance between efficacy and side effects. Indeed, other GLP-1-receptor agonists, such as the similarly structured liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.*, Victoza label at 2668 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose "to reduce gastrointestinal symptoms during initial titration."). Thus, a skilled artisan would be motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

Ex. 2551, ¶ 350.

PO's Citation 3: Efficacy

261. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have understood that the 1.6 mg dose was expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

190. Moreover, skilled artisans would have been aware of Novo Nordisk's phase I and phase II clinical trials testing once weekly doses ranging from 0.1-1.6 mg semaglutide. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. Similar to the liraglutide phase II study about which Seino reported that "[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy" (Ex. 1038 (Seino) at 6), skilled artisans would similarly expect that all of the once weekly doses of semaglutide tested in NCT657 and NCT773 would exhibit some degree of efficacy.

Ex. 1005,
¶¶ 190, 261.

349. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. In my opinion, these doses on the lower end of the range would still provide some degree of efficacy but would be suboptimal doses (*see* Seino at 166 ("[a]ll doses of liraglutide tested showed a degree of efficacy)). A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have understood that the 1.6 mg dose was expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Shargel at 577-78, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

Ex. 2551,
¶ 349.

Sanctions Are Inappropriate Here

Google LLC v. Hafeman,
IPR2022-01188, Paper 31, 29-31 (PTAB Dec. 7, 2023).

“[T]here’s never been a board decision that terminated a case because of a *Sotera* stipulation.”

Sanctions Are Inappropriate Here

Samsung Elecs. Co. v. Netlist, Inc.

IPR2022-00639, Paper 26 (PTAB Jan. 18, 2023);

Google LLC v. Hafeman,

IPR2022-01188, EX3001 (PTAB Mar. 20, 2023)

“Any dispute regarding the scope or alleged violation of stipulations proffered by a party should be addressed in the district court proceedings in which such stipulations are to have effect.”

Apple Inc. v. Maxell, Ltd.,

IPR2020-00204, Paper 21, 9-10 (PTAB Dec. 15, 2020)

“[T]o the extent Patent Owner believes Petitioner has violated the letter or spirit of its stipulation in the underlying litigation, Patent Owner could seek relief in the district court.”

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

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Patent Owner's Reasonable Expectation Criticisms are Misplaced

- Reasonable expectation of success when selecting prior art 1.0 mg dose, beyond “mere existence of trials”:

- Dosing schemes suggested “sweet spot” at 1.0 mg.

Ex. 1300, ¶¶ 295-311; Ex. 1301, ¶¶ 285-287, 297-298.

- POSA's knowledge of GLP-1's biological role.

Ex. 1003, ¶ 64; Ex. 1005, ¶¶ 76, 80, 87.

- Parent molecule, liraglutide, studied and described extensively.

Ex. 1003, ¶ 73.

- Liraglutide and semaglutide shared amino acids important for activity.

Ex. 1003, ¶¶ 78-79, 89-93; Ex. 1005, ¶ 84.

- Liraglutide's dose-response curve: “classic, sigmoidal dose-response profile,” showing more efficacy with higher doses.

Ex. 1005, ¶¶ 85-86, 238.

- This extra information is significant:

Salix Pharms., Ltd. v. Norwich Pharms. Inc., 98 F.4th 1056 (Fed. Cir. 2024).