

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

NOVO NORDISK A/S,
Patent Owner.

Case IPR2023-00724
Patent 10,335,462

**PATENT OWNER'S SUBMISSION OF UNRESOLVED
OBJECTIONS TO PETITIONER'S DEMONSTRATIVES**

Pursuant to 37 C.F.R. §42.70(b), and the Board’s August 14, 2024 Order Setting Oral Argument (Paper 78), Patent Owner Novo Nordisk A/S (“PO”) respectfully submits the below list of unresolved objections to Petitioner’s demonstratives. Following each objection is a copy of the objected-to slide with objectionable portions within red rectangles.

- **Slide 2:** This slide’s citations to EX1040, 1 and EX1039, 2 reflect reliance on new evidence, not supported by the citation to the brief on this slide.

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.

VICTOZA®
[VIC-tou-za]
(liraglutide (rDNA origin) injection)
Solution for Subcutaneous Use

• Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).

Ex. 1039 at 2;
Ex. 1003 at ¶¶ 74-75.

Pet. 16-17

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

2

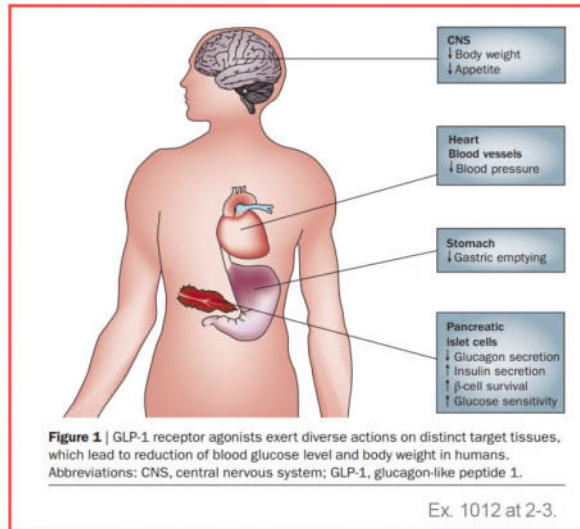
- **Slide 3:** This slide's citation to EX1012, Fig. 1 reflects reliance on new evidence, not supported by the citation to the brief on this slide.

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
AVO010	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
NV9535	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
Linaagliptin	2.5-5 mg once daily	I
Dulagliptin	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.



Ex. 1012 at 2-3.

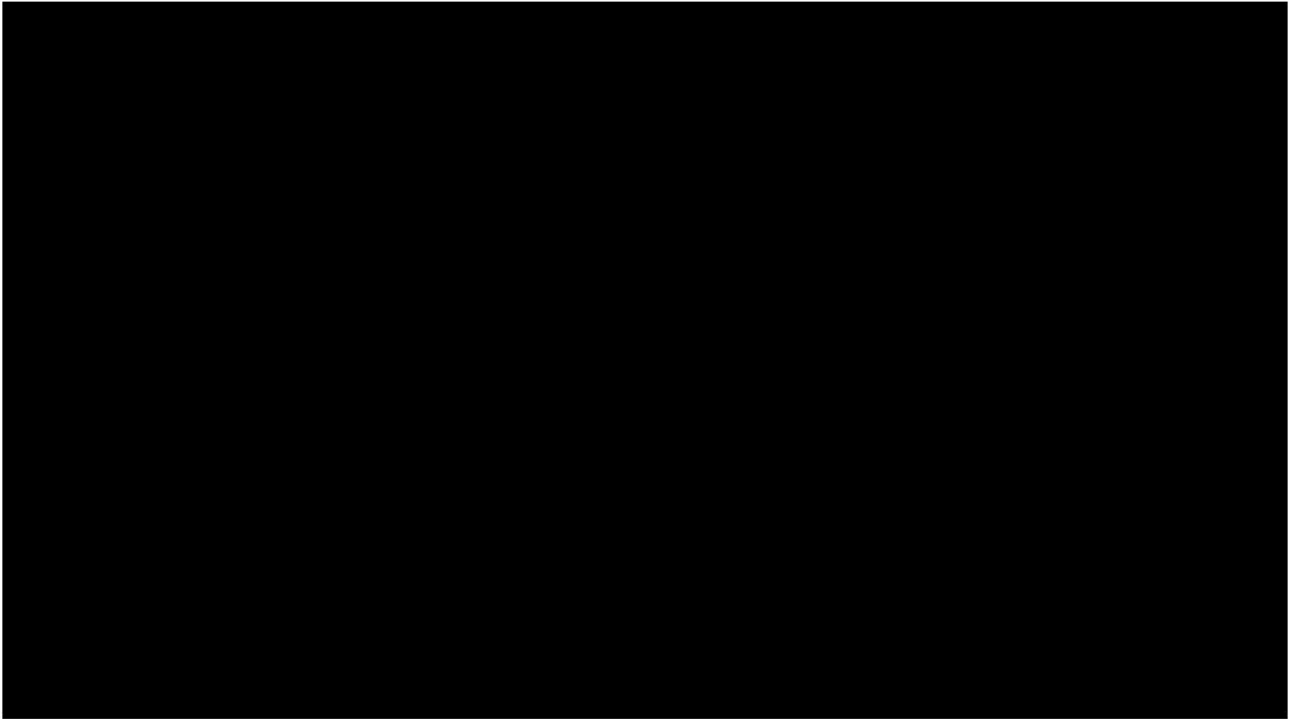
- **Slides 9-14:** These slides reflect new arguments regarding whether Dr. Jensen is properly named as an inventor of the '462 patent, which are not supported by the citations to the briefs on these slides.

Patent Owner Did Not Antedate WO421: No Earlier Conception by Jensen		
<i>Apator Miitors Aps v. Kamstrup A/S</i>, 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.”	<i>REG Synthetic Fuels, LLC v. Neste Oil Oyj</i>, 841 F.3d 954, 962 (Fed. Cir. 2016) (citation omitted) “Conception is ‘the formation, in the mind of the inventor of a <i>definite and permanent idea of the complete and operative invention, as it is thereafter to be applied in practice.</i>’”	<i>Burroughs Wellcome Co. v. Barr Laby's, Inc.</i>, 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.”

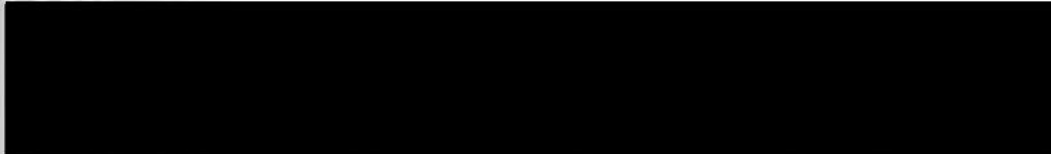
Pet. Reply 3-4

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

9



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



Apator Miitors Aps v. Kamstrup A/S,
887 F.3d 1293, 1297 (Fed. Cir. 2018)

“It is no answer that Apator’s evidence is ‘unrebutted,’ as Apator repeatedly points out. This criticism misunderstands Apator’s burden of proof under § 102(g), which requires that Apator prove Mr. Drachmann did conceive of his meter prior to Nielsen’s effective filing date, not that Kamstrup prove Mr. Drachmann did not.”

**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.’”

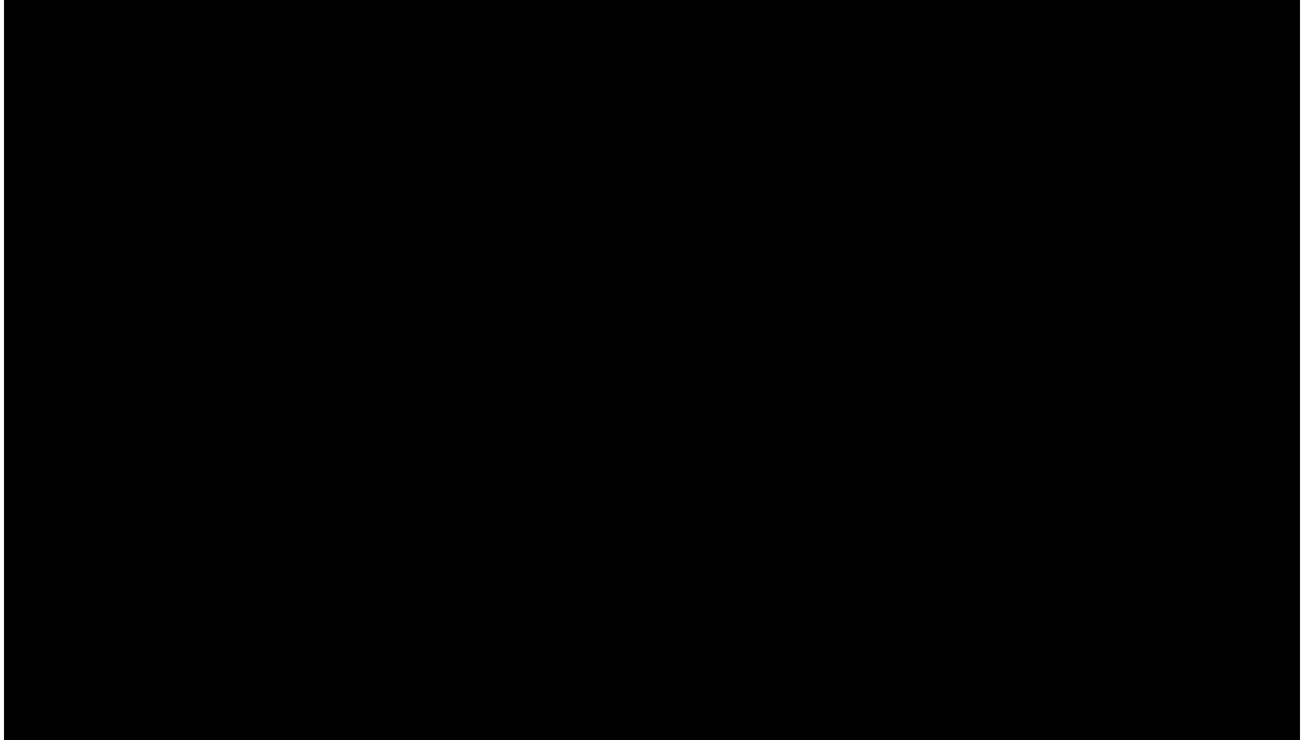
The inadequacy of UCSF’s showing is equally clear in the context of the specific interference counts. The limitations of the ‘719 count include specific concentrations, such as ‘0.01% to 1.0% of an azalide antibiotic’ and ‘0.1 to 10% of a polymeric suspending agent’ which is a water-swallowable water-insoluble 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.”

PO Sur-Reply 4

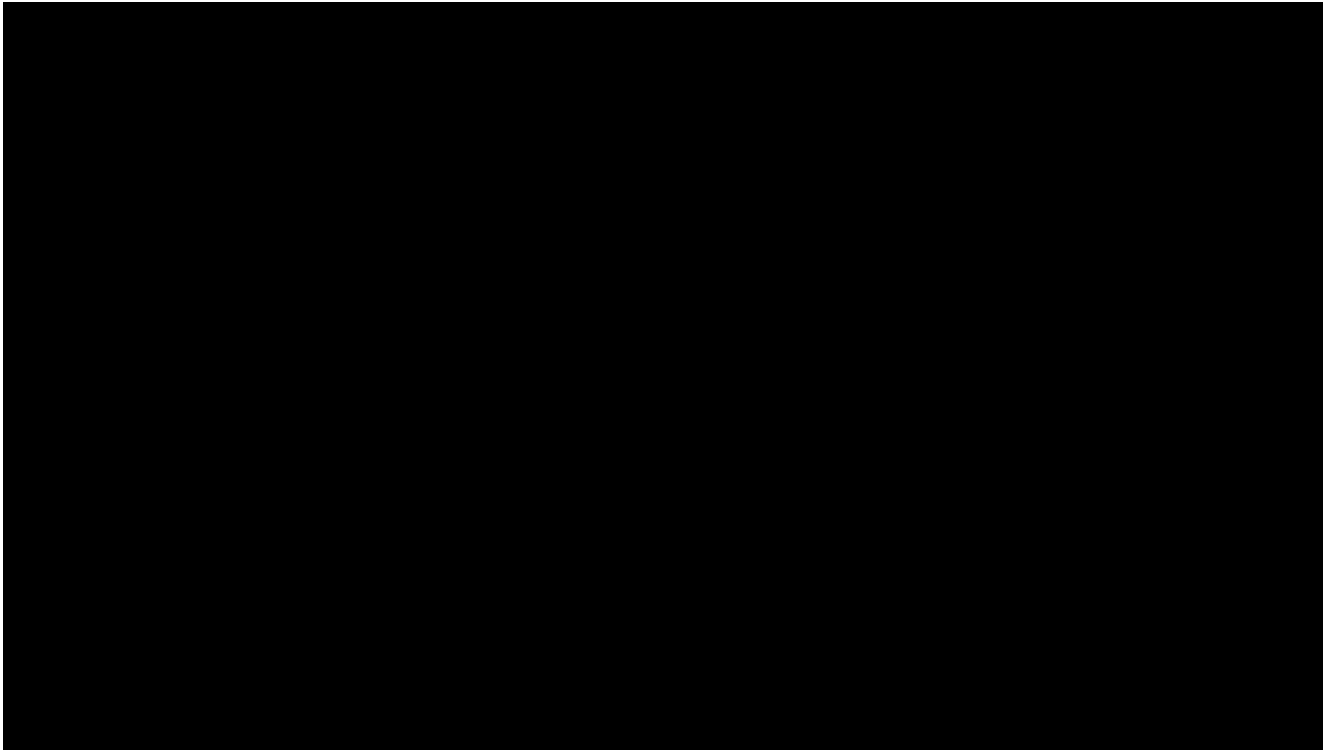
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

13

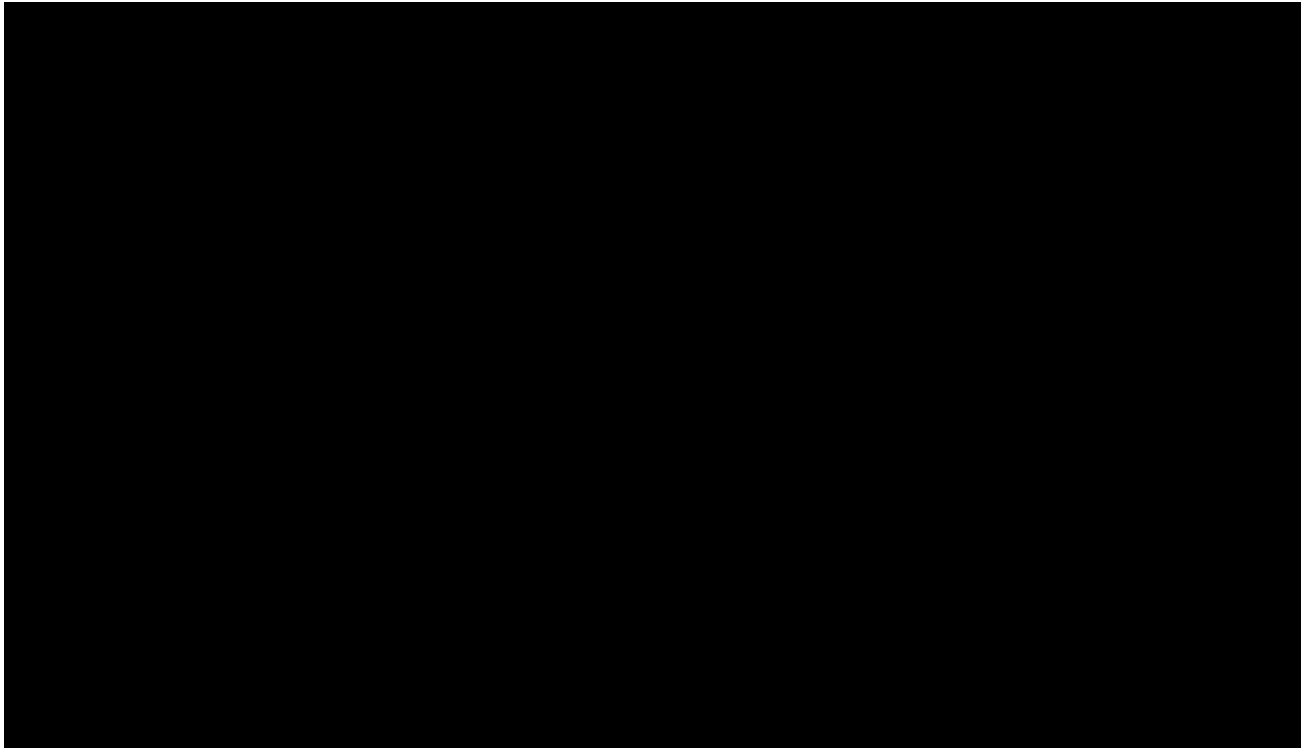
- **Slide 15:** The graphic reflecting on this slide reflecting two different excerpts from EX2028 is misleading and confusing.



- **Slide 16:** This slide includes a graphic reflecting two different excerpts from EX2030, which is misleading and confusing. Additionally, this slide's citation to this aspect of *NFC Technology, LLC v. Matal* reflects reliance on a new, unbriefed argument, not supported by the citations to the briefs on this slide.



- **Slide 17:** This slide's citation to EX2029 reflects reliance on new evidence, not supported by the citations to the briefs on the slide, and new arguments based on EX1312, 101:4-12, which are also not supported by the citations to the briefs on the slide.



- **Slide 31:** This slide fails to provide the context of the testimony presented (cutting off portions of an Answer that provide context).

WO421 Disclosed All Elements of Claim 1

1.0 mg once weekly

1.0 mg Once Weekly

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.).

1.0 mg is not "critical"

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.'"

Drug	Dose (mg)	HbA _{1c} (%)
Baseline	0.1	-0.5
Semaglutide	0.2	-0.58
Semaglutide	0.2	-0.9
Semaglutide	0.4	-1.1
Semaglutide	0.6	-1.46
Semaglutide	0.8	-1.44
Semaglutide	1.0	-1.69
Semaglutide	1.6	-1.69
Liraglutide	0.0	-1.18
Liraglutide	0.1	-1.34

Ex. 1001 (Fig. 1).

Pet. Reply 13-15

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

31

- **Slide 42:** This slide reflects reliance on a new, unbriefed argument regarding anticipation of '462 claim 3 by Lovshin other than by inherency, which is not supported by the citations to the briefs on this slide.

**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.

Pet. 35-36, 38; Pet. Reply 16-18

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

42

- **Slide 47:** This slide’s reliance on *In re Applied Materials, Inc.* for the proposition that “[a] recognition in the prior art that a property is affected by the variable is sufficient to find the variable result-effective” reflects reliance on *Applied Materials* for a new, unbriefed argument, which is not supported by the citations to the briefs on this slide.

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

Arm	Assigned Intervention
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 0.6 mg once weekly, s.c. injection
E: Experimental Intervention Drug semaglutide	Drug semaglutide 0.8 mg with insulin, once weekly, s.c. injection
F: Experimental Intervention Drug semaglutide	Drug semaglutide 0.8 mg with insulin, once weekly, s.c. injection

NCT773

A: Experimental	Drug NN0505 0.1 mg once weekly, s.c. injection
B: Experimental	Drug NN0505 0.2 mg once weekly, s.c. injection
C: Experimental	Drug NN0505 0.4 mg once weekly, s.c. injection
D: Experimental	Drug NN0505 0.6 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks, s.c. injection
E: Experimental	Drug NN0505 0.8 mg once weekly, s.c. injection
F: Experimental	Drug NN0505 0.6 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.0 mg once weekly for 6 weeks, s.c. injection
G: Experimental	Drug NN0505 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 administered 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 1.0 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

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

47

- **Slide 48:** This slide reflects reliance on a new, unbriefed argument that “[e]stablishing that a variable is result-effective is a low bar,” which is not supported by the citation to the brief on this slide.

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)

Pet. 41

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

48

- **Slide 49:** This slide's reliance on *Genentech Inc. v. Hospira, Inc.* for the proposition that "Petitioner's obviousness grounds do not require modifying any reference" reflects reliance on *Genentech* for a new, unbriefed argument, which is not supported by the citations to the briefs on this slide.

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)

Pet. 38-39; Pet. Reply 19-20

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

49

- **Slide 50:** This slide reflects reliance on a new, unbriefed argument that “[t]he semaglutide prior art dose range is not especially broad,” which is not supported by the citation to the brief on this slide.

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)

- **Slide 65:** The heading of this slide [REDACTED]
[REDACTED] contains a new, unbriefed argument not supported by the citation to the brief on this slide, and this slide's reliance on EX2300¶, 95 and EX2054, ¶¶58, 77, 78 in support of that argument reflects reliance on a new, unbriefed argument not supported by the citation to the brief on this slide.

- **Slide 66:** This slide reflects reliance on a new, unbriefed argument that “[a] nexus presumption cannot be founded on unclaimed features,” and this slide’s reliance on *Quanergy Systems, Inc. v. Velodyne Lidar USA, Inc.* in support of that argument reflects reliance on a new unbriefed argument, neither of which are supported by the citations to the briefs on this slide.

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)

PO Sur-Reply 27; Pet. Reply 34-35

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

66

- **Slide 68:** This slide's reliance on *Galderma Laboratories, L.P. v. Tolmar, Inc.*

as support for Petitioner's argument that "PO Did Not Meet its Commercial Success Production Burden" and "[h]owever, if the feature that creates the commercial success was known in the prior art, the success is not pertinent," reflects reliance on a new, unbriefed argument, which is not supported by the citation to the brief on this slide.

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."

Pet. Reply 19, 36-38 DEMONSTRATIVE EXHIBIT – NOT EVIDENCE 68

- **Slide 69:** This slide's citation to EX1003, ¶¶256, 298 reflects reliance on new evidence, not supported by the citations to the briefs on this slide.

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 <u>1.0 mg dose</u> 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.	
Pet. 20-23; Pet. Reply 36-37	DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
69	

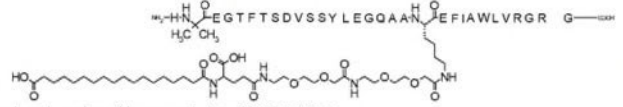
- **Slide 70:** This slide reflects reliance on a new, unbriefed argument that the '343 patent discloses once-weekly semaglutide, which is not supported by the citation to the brief on this slide.

The '343 Patent Disclosed Once Weekly Semaglutide to Treat T2D

(12) United States Patent
Lan et al.

(30) Patent No.:	US 8,129,343 B2	Date of Patent:	Mar. 6, 2012
(54) METHYLATED GLP-1 COMPOUNDS			
(75) Inventors:	Jeppu Lan, Erwin D.K. Fow-Bloch, Tansong D.K., Thomas Kwan-Hansen, Jorley D.K.	WO 2010/037111 WO 2010/042277 WO 2010/046279 WO 2010/048410 WO 2010/050501	6.2007 6.2007 6.2007 12.2007 8.2008
(75) Assignee:	Nova Nordisk A/S, (Registered D.K.)	WO 2010/050501 WO 2010/050502 WO 2010/050503 WO 2010/050504 WO 2010/050505	11.2008 11.2008 11.2008 11.2008 11.2008
(*) Note: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 682 days.			

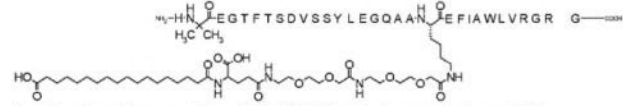
1. A compound of the structure



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).

Pet. Reply 16, 18, 36-38
DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
70

- **Slide 83:** This slide reflects reliance on a new, unbriefed argument that “PO’s attorney argument is not a substitute for expert analysis,” which is not supported by the citation to any brief.

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.

Drug	Dose	Weight Loss (kg)
Semaglutide	0.2 mg	-0.8
	0.4 mg	-1.8
	0.8 mg	-3.4
	1.6 mg	-4.8
Liraglutide	0.5 mg	-1.2
	1.2 mg	-2.6
	1.8 mg	-2.6

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.

DEMONSTRATIVE EXHIBIT – NOT EVIDENCE

83

- **Slide 84:** This slide's citation to EX2055, ¶38 reflects reliance on new evidence, not supported by the citation to any brief.

No Unexpected Results: Differences Merely of Degree

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

reference in kind in a "thick-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 (2.4kg)); 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

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- **Slide 95:** The heading of this slide (“*Sanofi v. Watson* Is Not a Range Case and Does Not Undermine REOS Here”) contains a new, unbriefed argument.

<i>Sanofi v. Watson</i> Is Not a Range Case and Does Not Undermine REOS Here	
POR at 59-60, discussing <i>Sanofi v. Watson Lab's Inc.</i>, 875 F.3d 636 (Fed. Cir. 2017). “In <i>Sanofi</i>, 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: <i>Sanofi v. Watson Lab's Inc.</i>, 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.”
POR 59-60	DEMONSTRATIVE EXHIBIT – NOT EVIDENCE
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Respectfully submitted,

Dated: August 26, 2024

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CERTIFICATE OF SERVICE

The undersigned hereby certifies that a copy of PATENT OWNER'S SUBMISSION OF UNRESOLVED OBJECTIONS TO PETITIONER'S DEMONSTRATIVES has been served in its entirety by causing the aforementioned document to be electronically mailed to the following attorneys of record for the Petitioner listed below:

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