

**IN THE UNITED STATES DISTRICT COURT
FOR THE DISTRICT OF DELAWARE**

IN RE: OZEMPIC (SEMAGLUTIDE)	)	MDL No. 22-3038-CFC
PATENT LITIGATION	)	
	)	
NOVO NORDISK INC. and NOVO NORDISK	)	
A/S,	)	
	)	
Plaintiffs,	)	C.A. No. 22-294-CFC
	)	CONSOLIDATED
v.	)	ANDA CASE
	)	
RIO BIOPHARMACEUTICALS INC., et al.,	)	
	)	~~CONFIDENTIAL~~
Defendants.	)	
NOVO NORDISK INC. and NOVO NORDISK	)	
A/S,	)	
	)	
Plaintiffs,	)	C.A. No. 22-1040-CFC
	)	
v.	)	
	)	
MYLAN PHARMACEUTICALS INC.,	)	
	)	
Defendant.	)	

DEFENDANTS’ SECOND SUPPLEMENTAL INVALIDITY CONTENTIONS

Pursuant to Paragraph 6 of the Scheduling Order, as modified (*see* D.I. 171), Defendants Dr. Reddy’s Laboratories, Ltd. and Dr. Reddy’s Laboratories, Inc. (“DRL”), Alvogen, Inc. (“Alvogen”), Rio Biopharmaceuticals Inc. and EMS S/A (collectively, “Rio”), Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Industries, Inc. (collectively, “Sun”), and Zydus Worldwide DMCC, Zydus Pharmaceuticals (USA) Inc., Zydus Lifesciences Limited, (collectively, “Zydus”), and Mylan Pharmaceuticals Inc. (“MPI”) (each individually a “Defendant Group” and collectively, “Defendants”) hereby submit to Plaintiffs Novo Nordisk Inc. and Novo

35 U.S.C. § 112, ¶ 1. “[T]he hallmark of written description is disclosure” and “requires an objective inquiry into the four corners of the specification” to determine whether it “show[s] that the inventor actually invented the invention claimed.” *Ariad Pharm., Inc. v. Eli Lilly & Co.*, 598 F.3d 1336, 1351 (Fed. Cir. 2010) (en banc).

Claim 2 of the ’953 patent states that the piston rod is locked in “at least one direction relative to the housing” leaving open the possibility that the piston rod is locked altogether and does not rotate. The ’953 patent specification fails to describe an injection pen satisfying each claim limitation where the piston rod does not rotate. Thus, claim 2 is invalid for lack of written description.

IX. INVALIDITY OF THE ’462 PATENT

A. Anticipation of the ’462 Patent

1. Claims 1 and 3 are Anticipated by WO ’421, NCT00696657, WO ’537 or Lovshin 2009

Claim 1 reads:

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 at col. 35 ll. 42-44.)

Claim 2 depends from claim 1 and adds the limitation “wherein the semaglutide is administered by parenteral administration;” claim 3 depends from claim 2 and adds the limitation “wherein the solution is administered by subcutaneous injection.” (*Id.* at col. 35 ll. 45-48.)

WO ’421

WO ’421 discloses “[m]ethods 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 administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” (WO ’421 at 1:4-7.) WO

'421 further discloses 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 33:20-22 (emphasis added).) Finally, WO '421's claim 17 discloses “[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* ..., said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist” and a DPP-4 inhibitor. *See id.* at 64:27-31 (emphasis added).

It could be noted that WO '421 described combined administration of semaglutide and a DPP-4 inhibitor “simultaneously, separately, sequentially or chronologically staggered,” and that the described “combination therapy may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.” *Id.* at 36:2-24; *see also id.* at 64:27-31 (claim 17). However, because claim 1 of the '462 patent uses the transitional term “comprising” (i.e., “comprising administering semaglutide once weekly in an amount of 1.0 mg”), WO '421's disclosure of treatment with both semaglutide and a DPP-4 inhibitor, in which each compound may be administered “prior to, concurrent to, or subsequent to” the other, falls within the scope of claim 1 of the '462 patent. Further, from WO '421 and other teachings in the art that semaglutide could be administered alone as a treatment for type 2 diabetes, a POSA reading WO '421 would have immediately envisioned administering semaglutide alone.

WO '421 discloses that, for the treatment of type 2 diabetes, “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” (WO '421 at 43:13.) A POSA would have understood that WO '421's disclosed range of semaglutide doses included a discrete dose of 1.0 mg. A POSA would not have viewed the disclosed range of doses in WO '421 (“0.1-1.6 mg”) to

be an infinite range determined without regard to the practicalities of methods of administration or to the available doses of existing GLP-1 receptor agonists. Instead, a POSA would have understood, for at least two reasons, that the disclosed range in WO '421 included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg.

First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram (i.e., dosing increments for Victoza were in increments of 0.6 mg (i.e., 0.6 mg, 1.2 mg, 1.8 mg).

Second, a POSA would have known that semaglutide was being tested in clinical trials before the priority date, including those using once weekly subcutaneous administration of semaglutide. *See, e.g.*, NCT00696657, NCT00851773.²⁰ A POSA would have known that in NCT00696657, semaglutide was tested at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (“1.6 mg with titration”), and that in NCT00851773, semaglutide was tested at doses of 0.1, 0.2, and 0.4 mg, 0.8 mg with titration, and 1.2 mg with titration. *Id.* Thus, the smallest dose step size used in each study was 0.1 mg, and the range of doses disclosed in WO '421 would include, at most, 16 options for dosing and a POSA would have immediately envisioned all the options in that range at the smallest reasonable step size. Therefore, WO '421's disclosure of 0.1 mg to 1.6 mg of semaglutide administered weekly anticipated the use of 1.0 mg semaglutide administered once weekly claimed in the '462 patent.

Finally, on dosing, a POSA would have immediately envisioned a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because a POSA would have understood that doses within the disclosed range of 0.1-1.6 mg were likely to

²⁰ <https://www.clinicaltrials.gov/study/NCT00851773?tab=history&a=6>

be effective, particularly doses at the upper end of the range. *See* NCT00696657, NCT00851773 (as of the priority date, semaglutide had been the subject of at least two clinical studies with dose ranges going from 0.1 mg up to, at most, 1.6 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg).

Regarding treating “a subject in need thereof,” WO ’421’s specification disclosed using a GLP-1 receptor in a method of treating type 2 diabetes. WO ’421 further disclosed that the method of treatment would be used with a patient in need of such treatment, including in patients who had not been treated previously. *See* WO ’421 at 7:34-10:6 (patients to be treated may be drug naïve, not having been treated before, patients who failed earlier therapy, or patients who are ineligible for another therapy), 10:14-20 (disclosed method of using a GLP-1 receptor agonist involves administering the compound “to the patient (particularly human patient) in need thereof, such as e.g a patient as described” in WO ’421), 10:22-11:32 (same), 12:15-20 (same), 13:5-7 (same); *see also, e.g., id.* at 64:27-31 (claim 17, reciting administering a GLP-1 receptor agonist in a method of treating type 2 diabetes).

Regarding the requirement of claim 2 that “semaglutide is administered by parenteral administration” and the requirement of claim 3 that the parenteral administration occurs “by subcutaneous injection,” WO ’421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. *Id.* at 35:23-36:5, 43:13. And, 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 (*see, e.g.,* Knudsen at 170:25-29),

making “subcutaneous injection” disclosed in WO ’421 a type of parenteral administration of a solution.

NCT00696657

NCT00696657 discloses a Phase 2 interventional trial wherein participants with type 2 diabetes mellitus “were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD).” (NCT00696657 at 2.)

In one of the arms of the trial disclosed by NCT00696657, semaglutide was used as a treatment for diabetes with “0.8 mg with titration, once weekly, [subcutaneous] injection.” (NCT00696657 at 3.) In a different arm of the trial, semaglutide was used as a treatment for diabetes with “1.6 mg with titration, once weekly, [subcutaneous] injection.” (*Id.*) The trial included treatment with semaglutide at six different dosages, including 0.8 and 1.6 mg. (*See id.*)

Arm ①	Intervention/treatment ①
Experimental: A	Drug: semaglutide 0.1 mg, once weekly, s.c. injection Other Name: NN9535
Experimental: B	Drug: semaglutide 0.2 mg, once weekly, s.c. injection Other Name: NN9535
Experimental: C	Drug: semaglutide 0.4 mg, once weekly, s.c. injection Other Name: NN9535
Experimental: D	Drug: semaglutide 0.8 mg, once weekly, s.c. injection Other Name: NN9535
Experimental: E	Drug: semaglutide 0.8 mg with titration, once weekly, s.c. injection Other Name: NN9535
Experimental: F	Drug: semaglutide 1.6 mg with titration, once weekly, s.c. injection Other Name: NN9535

(*Id.*)

WO '537

WO '537 discloses modified GLP-1 peptides for use in treating type 2 diabetes. (WO '537 at 22:24-29.) WO '537 also explains that such a composition “may be administered to a patient in need of such treatment.” (*Id.* at 32:32-33.) Moreover, Example 4 of WO '537 discusses semaglutide (*id.* at 47:4-22) as well as a patient with type 2 diabetes in need of treatment with a GLP-1 peptide, which improves glycemic control (*id.* at 22:24-26).

WO '537 discloses that the compounds according to the disclosure can be used to prepare a medicament for delaying, treating, or preventing disease progression for type 2 diabetes. (WO '537 at 38:3-4.) WO '537 further discloses that formulations can be prepared a variety of different

concentrations, such as from 0.1 mg/mL to 25 mg/mL. (*Id.* at 24:11-13.) WO '537 discloses once weekly administration of GLP-1 peptides, including semaglutide. “One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.” (*Id.* at 59:24-25.)

Pharmacokinetic Screening of Once Weekly GLP-1 Analogues

Pharmacokinetic screening of GLP-1 analogues for identification of suitable once weekly candidates were performed on candidates that according to the project screenings plan were shown to be sufficiently potent with respect to glucose lowering potential in a diabetic mouse model (db/db mice) and subsequently had a time of duration of 48 hours or more in the db/db mouse model.

(*Id.* at 59:28-32.) WO '537 further discloses that “[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.” (*Id.* at 34:15-16; *see also id.* at 34:3-4 (“Even more preferably, are controlled release and sustained release systems administered subcutaneous.”))

A POSA would have understood these to be disclosures of ranges of semaglutide doses including 1.0 mg once weekly. *See, e.g., Bristol-Myers Squibb Co.*, 246 F.3d at 1380 (“[T]he disclosure of a small genus may anticipate the species of that genus even if the species are not themselves recited.”); *ClearValue, Inc. v. Pearl River Polymers, Inc.*, 668 F.3d 1340, 1345 (Fed. Cir. 2012) (finding that prior art disclosure of genus “150 ppm or less” was sufficiently narrow to anticipate claims reciting “50 ppm or less.”). A subcutaneous injection is a form of parenteral administration. (*See, e.g.,* WO '537 at 34:15-16)

Lovshin 2009

Lovshin 2009 disclosed a “method for treating type 2 diabetes, comprising administering semaglutide.” In particular, Lovshin 2009 discloses investigation of the treatment of type 2 diabetes with the agent NN9535 by subcutaneous injection. (Lovshin 2009 at 263, and *id.* (Table

1).) NN9535 is and was known to be semaglutide. (See NCT00696657 at 3 (NN9535 is semaglutide).)

Lovshin 2009 notes that “incretins exert antidiabetic actions in a glucose-dependent manner,” and that NN9535 (semaglutide) is an “incretin-based therapy.” (*Id.* at 263, Table 1.) Lovshin 2009 further discloses that NN9535 (semaglutide) is a GLP-1 receptor agonist (like liraglutide and exenatide), *id.* at 263 (Table 1), and that “[c]ontinuous, 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,” *id.* at 262.

With respect to the claim element “comprising administering semaglutide,” Lovshin 2009 disclosed that semaglutide was “under active clinical investigation in phase I–II studies,” *id.* at 266, and a POSA would have known that phase I and II clinical studies involve administering treatments to patients. Lovshin 2009 also disclosed that liraglutide was administered once daily to patients with type 2 diabetes and was well tolerated and effectively reduced HbA_{1c} levels without hypoglycemia. *Id.* at 264. Further, Lovshin 2009 disclosed that “[a] 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight.” *Id.* In addition, Lovshin 2009 discloses that exenatide, the “first GLP-1 [receptor] agonist to be approved for human clinical use,” was used to treat patients with type 2 diabetes. *Id.* at 2. For at least these reasons, a POSA would have understood that semaglutide, like liraglutide, exenatide, and other GLP-1 receptor agonists, was administered to patients.

Lovshin 2009 discloses a dosage of “0.1–1.6 mg once weekly” semaglutide for treating type 2 diabetes mellitus, given by “subcutaneous injection.” (Lovshin 2009 at 263 (Table 1).) A POSA would have understood that the disclosed range of semaglutide doses in Lovshin 2009 included a discrete dose of 1.0 mg. A POSA would not have viewed the disclosed range of doses in Lovshin 2009 (“0.1-1.6 mg”) to be an infinite range determined without regard to the practicalities of methods of administration or to the available doses of existing GLP-1 receptor agonists. Instead, a POSA would have understood, for at least two reasons, that Lovshin 2009’s disclosed range included discrete dosing steps proceeding in increments of no less than 0.1 mg, including a step at 1.0 mg.

First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram (i.e., dosing increments for Victoza were in increments of 0.6 mg (i.e., 0.6 mg, 1.2 mg, 1.8 mg).

Second, a POSA would have known at least from Lovshin 2009 that the 0.1–1.6 mg dose range was, like other once weekly GLP-1 therapies, “being investigated” in Phase I/II studies. Lovshin 2009 at 263 (Table 1), 266. From this, a POSA would have known that there was an expectation that the effective clinical dose of semaglutide would reside within this disclosed limited range. At minimum, a POSA would have expected that a 1.0 mg dose could be administered for the purpose of care and management of a patient with Type 2 diabetes with a reasonable expectation of success.

Known prior art clinical trials testing once weekly subcutaneous administration of semaglutide would have confirmed this conclusion and expectation. *See, e.g.*, NCT00696657, NCT00851773. A POSA would have known that in NCT00696657, semaglutide was tested at

doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (“1.6 mg with titration”) and that in NCT00851773, semaglutide was tested at doses of 0.1, 0.2, and 0.4 mg, 0.8 mg with titration, and 1.2 mg with titration. *Id.* Thus, the smallest dose step size used in NCT00696657 and NCT00851773 was 0.1 mg, and the range of doses disclosed in Lovshin 2009 would include, at most, 16 options for dosing and a POSA would have immediately envisioned all the options in that range at the smallest reasonable step size. Therefore, Lovshin 2009’s disclosure of 0.1 mg to 1.6 mg of semaglutide administered weekly anticipated the use of 1.0 mg semaglutide administered once weekly claimed in the ’462 patent.

Finally, on dosing, a POSA would have immediately envisioned in Lovshin 2009 a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because a POSA would have understood that doses within the disclosed range of 0.1-1.6 mg were likely to be effective, particularly doses at the upper end of the range. *See* NCT00696657, NCT00851773 (as of the priority date, semaglutide had been the subject of at least two clinical studies with dose ranges going from 0.1 mg up to, at most, 1.6 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg).

Regarding treating “a subject in need thereof,” Lovshin 2009 discloses that incretins/GLP-1 receptor agonists like semaglutide are used in a method of treating type 2 diabetes. Lovshin 2009 further discloses that exenatide, “first GLP-1 [receptor] agonist to be approved for human clinical use,” as a treatment in patients with type 2 diabetes. Lovshin 2009 at 263. Lovshin 2009 also discloses that liraglutide was administered once daily to patients with type 2 diabetes and was well tolerated and effectively reduced HbA_{1c} levels without hypoglycemia. *Id.* at 264. Further, Lovshin 2009 discloses that “[a] 52-week study compared glimepiride monotherapy with liraglutide

monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight.” *Id.* A POSA would have known that a person with type 2 diabetes needed treatment.

Regarding the requirement of claim 2 that “semaglutide is administered by parenteral administration” and the requirement of claim 3 that the parenteral administration occurs “by subcutaneous injection,” Lovshin 2009 discloses that NN9535 (semaglutide) is administered by “subcutaneous injection.” Lovshin 2009 at 263 (Table 1). 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 (Knudsen at 170:25-29), and therefore that the “subcutaneous injection” Lovshin 2009 discloses is a type of parenteral administration of a solution.

Thus, WO ’421, NCT00696657, WO ’537, and Lovshin 2009 each explicitly or inherently disclose the methods for treating type 2 diabetes recited in claims 1 and 3 of the ’462 patent. *Eli Lilly & Co. v. Barr Labs et al.*, 251 F.3d 955, 971 (Fed. Cir. 2001) (Federal Circuit “case law firmly establishes that a later genus claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.”).

For at least these reasons, claims 1 and 3 are invalid as anticipated under 35 U.S.C. § 102. *See Akamai Techs., Inc. v. Cable & Wireless Internet Servs., Inc.*, 344 F.3d 1186, 1192 (Fed. Cir. 2003).

B. Obviousness of the '462 Patent

All of the claims of the '462 patent are invalid as obvious under 35 U.S.C. § 103(a) because the differences between the claimed subject matter and the prior art would have been obvious to a person of ordinary skill in the art before the effective filing date of this patent.

The prior art, taken as a whole, discloses, teaches, and/or suggests each and every element recited in the claims of the '462 patent. In addition, there was motivation to modify the prior art to arrive at the claimed inventions of the '462 patent, and to do so with a reasonable expectation of success.

A method of treatment claim does not require a lead compound analysis. *Novartis Pharms. Corp.*, 923 F.3d at 1060. Such claims are subject to the usual scrutiny under the Graham factors. *Id.* An examination of the *Graham* factors shows the obviousness of the '462 patent's claims, all of which are directed to a method of treating type 2 diabetes by a once-weekly administration of 1.0 mg semaglutide.

1. **Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 Patent and Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art**

a. Claims 1 and 3

Claim 1 reads:

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 at col. 35 ll. 42-44.)

Claim 2 depends from claim 1 and adds the limitation "wherein the semaglutide is administered by parenteral administration;" claim 3 depends from claim 2 and adds the limitation "wherein the solution is administered by subcutaneous injection." (*Id.* at col. 35 ll. 45-48.)

As of the relevant priority date, it was well known that GLP-1 analogues such as semaglutide could be therapeutically useful for treating type 2 diabetes. WO '421 discloses “[m]ethods 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 administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” (WO '421 at 1:4-7.) NCT00696657 discloses a Phase 2 interventional trial entitled “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.” (NCT00696657 at 2.) Under “Condition or disease,” NCT00696657 identifies both “Diabetes” and “Diabetes Mellitus, Type 2.” (*Id.*) Lovshin 2009 discloses that “[i]ncretin-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.” (Lovshin 2009 at 262.)

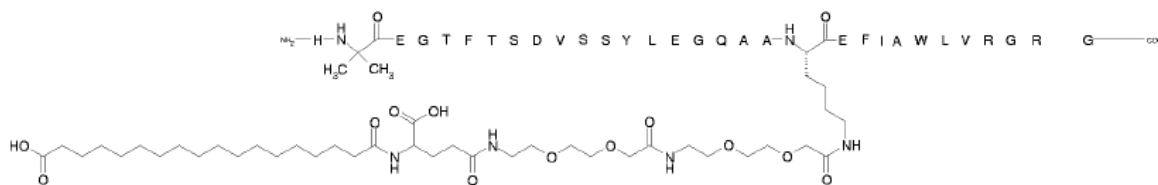
WO '537 (or US '478 or the '343 patent) discloses “[a]n embodiment provides the use of a [GLP-1] compound according to any one of the embodiments . . . for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” (WO '537 at 22:24 – 23:3; US '478 at [0129]-[0130]; '343 patent at col. 40 ll. 36-48.) WO '537 (or US '478 or the '343 patent) further discloses, “[i]n one embodiment a compound according to the invention is used for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity” (WO '537 at 37:34-36; US '478 at [0191]; '343 patent at col. 53 ll. 4-7.)

WO '421 discloses 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,” each of which was disclosed to have “significant sequence identity to GLP-1.” (WO '421 at 33:20-26 (emphasis added).) NCT00696657 further discloses that trial “participants were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD).” (NCT00696657 at 2; *see also* WO '421 at 43:7-19 (disclosing overlapping dosage amounts for several GLP-1 receptor agonists, including liraglutide and semaglutide).) Lovshin 2009 discloses investigation of the treatment of type 2 diabetes with the agent NN9535 by subcutaneous injection. (Lovshin 2009 at 263 (Table 1).) NN9535 is and was known to be semaglutide. (*See* NCT00696657 (NN9535 is semaglutide).)

WO '537 (or US '478 or the '343 patent) is directed to therapeutic peptides, i.e., new protracted GLP-1 compounds. (WO '537 at 1:5-6; US '478 at [0001]; '343 patent at col. 1 ll. 16-17.) Specifically, WO '537 (or US '478 or the '343 patent) discloses the structure of semaglutide.

Example 4

N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



(WO '537 at 47:4-8; US '478 at [0265]; '343 patent at col. 61 ll. 1-28.)

WO '537 (or US '478 or the '343 patent) discloses once weekly administration of GLP-1 peptides, including semaglutide. “One aspect of this invention is to prepare GLP-1

analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.” (WO ’537 at 59:24-25; US ’478 at [0354]; ’343 patent at col. 94 ll. 45-47.)

Pharmacokinetic Screening of Once Weekly GLP-1 Analogues

Pharmacokinetic screening of GLP-1 analogues for identification of suitable once weekly candidates were performed on candidates that according to the project screenings plan were shown to be sufficiently potent with respect to glucose lowering potential in a diabetic mouse model (db/db mice) and subsequently had a time of duration of 48 hours or more in the db/db mouse model.

(WO ’537 at 59:28-32; US ’478 at [0355]; ’343 patent at col. 94 ll. 50-58.)

WO ’537 (or US ’478 or the ’343 patent) further discloses that “[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.” (WO ’537 at 34:15-16; US ’478 at [0175]; ’343 patent at col. 50 ll. 29-31; *see also* WO ’537 at 34:3-4 (“Even more preferably, are controlled release and sustained release systems administered subcutaneous.”); US ’478 at [0174] (same); ’343 patent at col. 50 ll. 11-12 (same).)

The ’833 patent also discloses:

[I]n a preferred embodiment, the formulations of the invention are to be administered parenterally to a patient in need thereof. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe.

(’833 patent at col. 13 ll. 45-50.)

Madsbad 2011 discloses that the “once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes.” (Madsbad 2011 at 394.)

Madsbad 2011 discloses dosing regimens for several GLP-1 receptor agonists, including semaglutide, which is administered by subcutaneous (sc) injection:

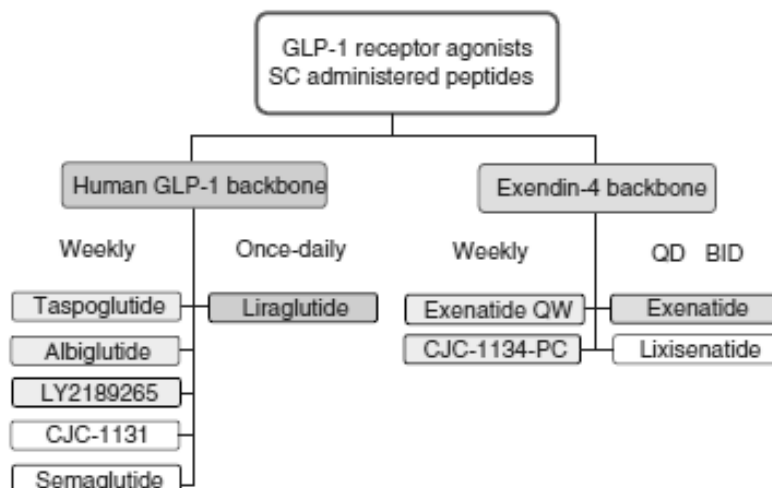


Figure 1. Shows the glucagon-like peptide-1 (GLP-1) receptor agonists, which have already been approved (exenatide BID and liraglutide). The agonists are subdivided in relation to whether the backbone of the compound is human GLP-1 or exenatide, and in relation to the frequency of administration (once weekly or once daily or twice daily). The once-weekly GLP-1 receptor agonists illustrated with yellow are discussed in details in the present review.

(*Id.* at 395.)

Madsbad 2011 discloses that “[i]ncretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been introduced into clinical practice. . . . Several once-weekly GLP-1 receptor agonists are in phase 3 development.” (*Id.* at 394.)

WO '421 discloses that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” (WO '421 at 43:13.) NCT00696657 discloses that trial “participants were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD).” (NCT00696657 at 2.) The NCT00696657 trial included treatment with semaglutide at six different dosages, including 0.8 and 1.6 mg. (*See id.* at 3.)

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

(*Id.* (disclosing administration of semaglutide once weekly by subcutaneous injection).) Lovshin 2009 discloses treatment at a dosage of 0.1 to 1.6 mg semaglutide once per week. (Lovshin 2009 at 263 (Table 1).) WO '537 (or US '478 or the '343 patent) further discloses that formulations can be prepared a variety of different concentrations, such as from 0.1 mg/mL to 25 mg/mL. ('537 at 24:11-13; US '478 at [144]; '343 patent at col. 41 ll. 60-63.)

A POSA would have understood these to be disclosures of ranges of semaglutide doses including 1.0 mg once weekly. *See Bristol-Myers Squibb*, 246 F.3d at 1380; *ClearValue*, 668 F.3d at 1345. Alternatively, the dosage range disclosed by Lovshin 2009 renders the claimed 1.0 mg dosage obvious. By routine testing of this range of dosages, 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. *See In re Peterson*, 315 F.3d 1325, 1329-30 (Fed. Cir. 2003) (“A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art. . . . In fact, when, as here, the claimed ranges are completely encompassed by the prior art, the conclusion is even more compelling than in cases of mere overlap. 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

percentage ranges is the optimum combination of percentages.”); *E.I. DuPont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1006 (Fed. Cir. 2018) (“For decades, [the Federal Circuit] and its predecessor have recognized that where the general conditions of a claim are disclosed in the prior art, it is not inventive to discover the optimum or workable ranges by routine experimentation.”) (internal quotation omitted); *see also Valeant Pharms. Int’l, Inc. v. Mylan Pharms. Inc.*, 955 F.3d 25, 31 (Fed. Cir. 2020) (“[T]his court [has] recognized that ‘[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.’”) (quoting *In re Peterson*, 315 F.3d at 1329); *see also In re Aller*, 220 F.2d 454, 458 (C.C.P.A. 1955) (“No invention is involved in discovering optimum ranges of a process by routine experimentation.”).

The ability of a POSA to determine an optimal dosage from a range is reinforced by the ’833 patent, which discloses:

[I]t is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. . . . It is to be understood that “an effective amount” is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. *diabetes*, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.) presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

(’833 patent at col. 13 l. 60 – col. 14 l. 15 (emphasis added).)

A POSA would have known how to formulate a semaglutide solution suitable for subcutaneous injection. For example, WO ’421 discloses:

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.

(*Id.* at 39:23-26.) Moreover, a POSA would have been aware of knowledge in the art regarding subcutaneous pharmaceutical formulations. (See, e.g., WO '537 at 63:10-15 (disclosing an exemplary semaglutide formulation with a concentration of 6.25 mg/ml semaglutide); US '478 at [0385] (same); '343 patent at col. 98 ll. 1-8 (same); WO '537 at 5:32-35 (disclosing pharmaceutical formulations comprising GLP-1 compounds, such as semaglutide, along with excipients); US '478 at [0031] (same); '343 patent at col. 4 ll. 57-62 (same).)

WO '537 (or US '478 or the '343 patent) discloses that “[c]ompositions of the current invention are specifically useful in formulation of controlled, sustained, protracting, retarded and slow release drug delivery systems. More specifically, but not limited to, compositions are useful in formulation of parenteral controlled release and sustained release systems.” (WO '537 at 33:35 – 34:2; US '478 at [0174]; '343 patent at col. 50 ll. 4-9.)

A POSA would have been motivated to combine the teachings of WO '421, NCT00696657, Lovshin 2009, WO '537,²¹ the '833 Patent, and Madsbad 2011 because they are all directed to the use of GLP-1 agonists, including semaglutide, for the treatment of diabetes, including in parenteral formulations for subcutaneous injection.

A POSA viewing the teachings of WO '421, NCT00696657, and/or Lovshin 2009, optionally in view of one or more of WO '537, the '833 Patent, and Madsbad 2011, in light of the POSA's knowledge would have been motivated with a reasonable expectation of success to utilize parenteral administration of 1.0 mg semaglutide by subcutaneous injection once weekly for the treatment of type 2 diabetes.

²¹ “WO '537” refers to WO '537 or US '478 or the '343 patent, here and below.

Claims 1 and 3 of the '462 patent thus claim nothing more than the use of an old compound for a known purpose at a dose that falls within the prior art-disclosed range. That cannot make the claims nonobvious. *See Galderma Lab'ys, L.P. v. Tolmar, Inc.*, 737 F.3d 731, 737 (Fed. Cir. 2013); *see also id.* at 738 (“[W]here 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.”).

For at least these reasons, claims 1 and 3 are invalid under 35 U.S.C. § 103 as obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of the '833 Patent and Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

b. Claim 4 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with the '833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

Claim 4 depends from claim 1 and adds the limitation “wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.” ('462 patent at col. 35 ll. 49-52.)

The '833 patent claims “[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to 10.0.” ('833 patent at col. 22 ll. 48-54 (claim 1).) A POSA would have understood that a disodium phosphate dihydrate buffer is an example of a phosphate buffer.

The '833 patent further claims “[t]he formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.” (*Id.* at col. 22 ll. 66-67 (claim 6).) Examples 1-6 of the '833 patent (each exemplary formulation) further disclose the use of a phosphate buffer at pH within the range of 7.0-9.0. (*Id.* at col. 15 l. 66 – col. 22 l. 21.)

The '833 publication further discloses:

Where a buffer is to be included in the formulations of the invention, the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof. . . . In a preferred embodiment of the invention, the buffer is glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate or mixtures thereof.

(*Id.* at col. 10 ll. 47-57.)

The '833 patent also discloses that “[t]he inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known.” (*Id.* at col. 1 ll. 30-31.) The POSA would have known that semaglutide is a peptide.

Example 3 of the '833 patent teaches that “[i]t is believed that similar results [*i.e.*, ‘no clogging of the needles’] to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90” and discloses a pH of “7.40, 7.70, 7.90, or 8.15.” (*Id.* at col. 20 ll. 6-19.) In Example 4, the '833 patent discloses a liraglutide composition with a pH of 7.40 containing sodium dihydrogen phosphate. (*Id.* at col. 20 ll. 29-35.) Example 5 of the '833 patent also discloses a composition with a pH of 7.4. (*Id.* at col. 20 l. 67.)

WO '537 (or US '478 or the '343 patent) discloses pharmaceutical formulations comprising GLP-1 compounds, such as semaglutide, along with excipients:

The term “pharmaceutical composition” as used herein means a product comprising an active compound or a salt thereof together with pharmaceutical excipients such as buffer, preservative, and optionally a tonicity modifier and/or a stabilizer. Thus a pharmaceutical composition is also known in the art as a pharmaceutical formulation.

(WO '537 at 5:32-35; US '478 at [0031]; '343 patent at col. 4 ll. 57-62.)

Another object of the present invention is to provide a pharmaceutical formulation comprising a compound according to the present invention which is present in a concentration from 0.1 mg/ml to 25 mg/ml, and wherein said formulation has a pH from 3.0 to 9.0. The formulation may further comprise a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants. In one embodiment of the invention the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water.

(WO '537 at 24:11-16; US '478 at [0144]; '343 patent at col. 41 l. 60 – col. 42 l. 38.)

Exemplary pH ranges are provided in WO '537, US '478, and the '343 patent:

In another embodiment of the invention the pH of the formulation is from about 7.0 to about 9.5. In another embodiment of the invention the pH of the formulation is from about 3.0 to about 7.0. In another embodiment of the invention the pH of the formulation is from about 5.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 9.0. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 8.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.0. In another embodiment the pharmaceutical formulation is from 8.0 to 8.5.

(WO '537 at 24:30 – 25:2; US '478 at [0148]; '343 patent at col. 42 l. 59 – col. 43 l. 4.)

WO '537 (or US '478 or the '343 patent) also discloses:

In a further embodiment of the invention the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, bicine, tricine, malic acid, succinate, maleic acid, fumaric acid, tartaric acid, aspartic acid or mixtures thereof.

(WO '537 at 25:4-8; US '478 at [0149]; '343 patent at col. 43 ll. 5-11.) Further, WO '537 (or US '478 or the '343 patent) provides a specific example of a pharmaceutical formulation comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15.

Pharmaceutical formulation:

A compound of the invention may be formulated as:

Compound of example 4 6,25 mg/ml

Propyleneglycol 14,0 mg/ml

Phenol 5.5 mg/ml

Phosphate Buffer pH 8.15

(WO '537 at 63:10-15; US '478 at [0385]; '343 patent at col. 98 ll. 1-8.)

The '833 patent also discloses:

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

('833 patent at col. 12 l. 64 – col. 13 l. 3.)

As described above with respect to claims 1-3, as of the earliest priority date to which the claims of the '462 patent may be entitled, a POSA would have been motivated with a reasonable expectation of success to treat type 2 diabetes by administering semaglutide by subcutaneous injection, a form of parenteral administration, once weekly in an amount of 1.0 mg to a subject in need thereof. In light of the prior art disclosures described here, a POSA would have been further motivated to formulate this subcutaneous injection as an isotonic aqueous solution, including a phosphate buffer at a pH in the range of 7.0-9.0. The prior art discloses semaglutide formulation pH ranges that substantially overlap with the claimed pH values recited in the dependent claims of the '462 patent. *Valeant Pharms. Int'l, Inc.*, 955 F.3d at 31 (“[T]his court [has] recognized that

‘[a] *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.’”) (quoting *In re Peterson*, 315 F.3d at 1329). A POSA would have had a reasonable expectation of success in making such a formulation using conventional techniques of the pharmaceutical industry as taught in the ’833 patent. (See ’833 patent at col. 12 l. 64 – col. 13 l. 3.)

For at least these reasons, and the reasons discussed above with respect to claims 1-3, claim 4 is invalid under 35 U.S.C. § 103 as obvious over WO ’421, NCT00696657, WO ’537 and/or Lovshin 2009 in combination with one or more of WO ’537 and the ’833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

c. Claim 5 is obvious over WO ’421, NCT00696657, WO ’537 and/or Lovshin 2009 in combination with the ’833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

Claim 5 depends from claim 4 and adds the limitation “wherein the solution further comprises propylene glycol and phenol.” (’462 patent at col. 35 ll. 53-54.)

The ’833 patent claims “[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to 10.0.” (’833 patent at col. 22 ll. 48-54 (claim 1).)

The ’833 patent further discloses the use of propylene glycol as an isotonicity agent in aqueous solutions containing GLP-1 agonists. (See *id.* at col. 24 ll. 7-14 (claim 23); see also *id.* at col. 19 l. 44 (disclosing the use of propylene glycol as an isotonicity agent).) Semaglutide is a GLP-1 agonist.

The '833 patent discloses that “[t]he use of a preservative in pharmaceutical compositions is well-known to the skilled person. (*Id.* at col. 11 ll. 6-7.)

The '833 patent further discloses the use of “phenol (5.0 or 5.5 mg/ml)” as a preservative. (*Id.* at col. 20 l. 13.) The '833 patent also discloses that “[i]n a preferred embodiment of the invention the preservative is phenol or m-cresol.” (*Id.* at col. 10 ll. 65-67.)

The '833 patent discloses:

[T]he present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. . . . [T]he present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

(*Id.* at col. 1 ll. 33-45.)

The '833 patent further discloses “that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices.” (*Id.* at col. 1 ll. 53-57; *see also id.* at col. 13 ll. 43-45 (Disclosing “the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular.”).)

The '833 patent also discloses that “[t]he present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.” (*Id.* at col. 2 ll. 58-62.)

WO '537 (or US '478 or the '343 patent) discloses “[i]n a further embodiment of the invention the formulation further comprises a pharmaceutically acceptable preservative. In a further embodiment of the invention the preservative is selected from the group consisting of phenol” (WO '537 at 25:11-13; US '478 at [0150]; '343 patent at col. 43 ll. 14-17.) WO

'537 (or US '478 or the '343 patent) further discloses that in “an embodiment the isotonicity agent is propyleneglycol.” (WO '537 at 25:34-35; US '478 at [0151]; '343 patent at col. 43 ll. 47-48.) Further, specific examples are provided of pharmaceutical formulations comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15.

Pharmaceutical formulation:

A compound of the invention may be formulated as:

Compound of example 4 6,25 mg/ml

Propyleneglycol 14,0 mg/ml

Phenol 5.5 mg/ml

Phosphate Buffer pH 8.15

(WO '537 at 63:10-15; US '478 at [0385]; '343 patent at col. 98 ll. 1-8.)

The '833 patent discloses:

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

('833 patent at col. 12 l. 64 – col. 13 l. 3.)

As described above with respect to claims 1-4, as of the earliest priority date to which the claims of '462 patent may be entitled, a POSA would have been motivated with a reasonable expectation of success to treat type 2 diabetes by administering semaglutide by subcutaneous injection, a form of parenteral administration, once weekly in an amount of 1.0 mg to a subject in need thereof. A POSA would have been further motivated to formulate this subcutaneous injection as an isotonic aqueous solution including a phosphate buffer at a pH in the range of 7.0-9.0. In light of the prior art disclosures described here, a POSA would have been further motivated to formulate the isotonic aqueous solution to include propylene glycol and phenol and would have

reasonably expected such a formulation to prevent clogging of the injection device. A POSA would have had a reasonable expectation of success in making such a formulation using conventional techniques of the pharmaceutical industry based on the teachings of the '833 patent. (*See id.*)

For at least these reasons, and the reasons discussed above with respect to claims 1-4, claim 5 is invalid under 35 U.S.C. § 103 as obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with the '833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

d. Claim 7 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with the '833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

Claim 6 depends from claim 4 and adds the limitation “wherein the pH is 7.4.” ('462 patent at col. 36 ll. 40-41.) Claim 7 depends from claim 6 and adds the limitation “wherein the solution further comprises propylene glycol and phenol.” ('462 patent at col. 36 ll. 42-43.)

Example 3 of the '833 patent teaches that “[i]t is believed that similar results [*i.e.*, ‘no clogging of the needles’] to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90” and discloses a pH of “7.40, 7.70, 7.90, or 8.15.” ('833 patent at col. 20 ll. 6-19.) In Example 4, the '833 patent discloses a liraglutide composition with a pH of 7.40 containing sodium dihydrogen phosphate. (*Id.* at col. 20 ll. 29-35.) Example 5 of the '833 patent also discloses a composition with a pH of 7.4. (*Id.* at col. 20 l. 67.)

WO '471 discloses the use of a parenteral formulation of semaglutide for the treatment of type 2 diabetes comprising propylene glycol, phenol, and a disodium hydrogen phosphate buffer at pH 7.4. (*See* WO '471 at 18:7-19, 24:30-31.)

The '833 patent claims “[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to 10.0.” ('833 patent at col. 22 ll. 48-54 (claim 1).)

The '833 patent further claims “[t]he formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.” (*Id.* at col. 22 ll. 66-67 (claim 6).) Examples 1-6 of the '833 patent (each exemplary formulation) further disclose the use of a phosphate buffer at pH within the range of 7.0-9.0. (*Id.* at col. 15 l. 66 – col. 22 l. 21.)

Exemplary pH ranges are provided in WO '537 (or US '478 or the '343 patent):

In another embodiment of the invention the pH of the formulation is from about 7.0 to about 9.5. In another embodiment of the invention the pH of the formulation is from about 3.0 to about 7.0. In another embodiment of the invention the pH of the formulation is from about 5.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 9.0. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 8.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.0. In another embodiment the pharmaceutical formulation is from 8.0 to 8.5.

(WO '537 at 24:30 – 25:2; US '478 at [0148]; '343 patent at col. 42 l. 59 – col. 43 l. 4.)

The '833 patent also discloses:

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

('833 patent at col. 12 l. 64 – col. 13 l. 3.)

As described above with respect to claims 1-4, as of the earliest priority date to which the claims of the '462 patent may be entitled, a POSA would have been motivated with a reasonable expectation of success to treat type 2 diabetes by administering semaglutide by subcutaneous injection, a form of parenteral administration, once weekly in an amount of 1.0 mg to a subject in need thereof. A POSA would have been further motivated to formulate this subcutaneous injection as an isotonic aqueous solution including a phosphate buffer at a pH in the range of 7.0-9.0. In light of the prior art disclosures described here, a POSA would have been further motivated to formulate the isotonic aqueous solution at pH 7.4 and would have reasonably expected such a formulation to prevent clogging of the injection device. (See WO '530 at 143-44 (Expressing the goal of creating a pharmaceutical composition for parenteral administration that is "isotonic with the blood of the intended recipient."); Raymond Chang, *Chemistry 724* (10th ed. 2010) (7.4 is the pH of blood); Shu-Hua Kuo et al., *Role of pH Value in Clinically Relevant Diagnosis*, 10 *Diagnostics* 106, 107 (2020) (the pH of subcutaneous tissue is 7.4) (citing J.R. Sharpe et al., *The Effect of PH in Modulating Skin Cell Behaviour*, 161 *Br. J. Dermatology*, 671 (2009)).) A POSA would have had a reasonable expectation of success in making such a formulation using conventional techniques of the pharmaceutical industry based on the teachings of the '833 patent. (See '833 patent at col. 12 l. 64 – col. 13 l. 3.) The disclosed pH ranges, including 6.0-7.5, are sufficiently narrow to constitute a disclosure of pH 7.4, *Bristol-Myers Squibb*, 246 F.3d at 1380; *ClearValue*, 668 F.3d at 1345, or alternatively render it obvious, *In re Peterson*, 315 F.3d at 1329-30; *E.I. DuPont de Nemours*, 904 F.3d at 1006.

Regarding the additional subject matter recited in claim 7, the '833 patent claims "[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation

in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to 10.0.” (’833 patent at col. 22 ll. 48-54 (claim 1).)

The ’833 patent further discloses the use of propylene glycol as an isotonicity agent in aqueous solutions containing GLP-1 agonists. (*See id.* at col. 24 ll. 7-14 (claim 23); *see also id.* at col. 19 l. 44 (disclosing the use of propylene glycol as an isotonicity agent).) Semaglutide is a GLP-1 agonist.

The ’833 patent discloses that “[t]he use of a preservative in pharmaceutical compositions is well-known to the skilled person. (*Id.* at col. 11 ll. 6-7.)

The ’833 patent further discloses the use of “phenol (5.0 or 5.5 mg/ml)” as a preservative. (*Id.* at col. 20 l. 13.) The ’833 patent also discloses that “[i]n a preferred embodiment of the invention the preservative is phenol or m-cresol.” (*Id.* at col. 10 ll. 65-67.)

The ’833 patent discloses:

[T]he present inventors have observed that mannitol causes problems during the production of peptide formulations as it crystallizes resulting in deposits in the production equipment and in the final product. . . . [T]he present inventors have observed that in peptide formulations to be administered by injection, the presence of mannitol results in clogging of injection devices.

(*Id.* at col. 1 ll. 33-45.)

The ’833 patent further discloses “that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices.” (*Id.* at col. 1 ll. 53-57; *see also id.* at col. 13 ll. 43-45 (Disclosing “the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular.”).)

The ’833 patent also discloses that “[t]he present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises

replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.” (*Id.* at col. 2 ll. 58-62.)

WO '537 (or US '478 or the '343 patent) discloses “[i]n a further embodiment of the invention the formulation further comprises a pharmaceutically acceptable preservative. In a further embodiment of the invention the preservative is selected from the group consisting of phenol” (WO '537 at 25:11-13; US '478 at [0150]; '343 patent at col. 43 ll. 14-17.) WO '537 (or US '478 or the '343 patent) further discloses that in “an embodiment the isotonicity agent is propyleneglycol.” (WO '537 at 25:34-35; US '478 at [0151]; '343 patent at col. 43 ll. 47-48.) Further, specific examples are provided of pharmaceutical formulations comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15.

Pharmaceutical formulation:

A compound of the invention may be formulated as:

Compound of example 4 6,25 mg/ml

Propyleneglycol 14,0 mg/ml

Phenol 5.5 mg/ml

Phosphate Buffer pH 8.15

(WO '537 at 63:10-15; US '478 at [0385]; '343 patent at col. 98 ll. 1-8.)

The '833 patent discloses:

The formulations of the invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Remington: *The Science and Practice of Pharmacy*, 19th edition, 1995, where such conventional techniques of the pharmaceutical industry involve dissolving and mixing the ingredients as appropriate to give the desired end product.

('833 patent at col. 12 l. 64 – col. 13 l. 3.)

As described above with respect to claims 1, 3, 4, and 5, as of the earliest priority date to which the claims of '462 patent may be entitled, a POSA would have been motivated, with a

reasonable expectation of success, to treat type 2 diabetes by administering semaglutide by subcutaneous injection, a form of parenteral administration, once weekly in an amount of 1.0 mg to a subject in need thereof. A POSA would have been further motivated to formulate this subcutaneous injection as an isotonic aqueous solution including a phosphate buffer at pH 7.4. In light of the prior art disclosures described here, a POSA would have been further motivated to formulate the isotonic aqueous solution to include propylene glycol and phenol and would have reasonably expected such a formulation to prevent clogging of the injection device. A POSA would have had a reasonable expectation of success in making such a formulation using conventional techniques of the pharmaceutical industry based on the teachings of the '833 patent. (*See id.*)

For at least these reasons, and the reasons discussed above with respect to claims 1-4 and 6, claim 7 is invalid under 35 U.S.C. § 103 as obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with the '833 Patent, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

2. Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent

a. Claim 1

Claim 1 of the '462 patent recites “[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.” Claim 1 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent.

- i. A skilled artisan would have been motivated to pursue the method recited in claim 1

The disclosures of WO '421 are described above.

WO '421 disclosed “methods 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 administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO '421 at 1:4-7. WO '421 further 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 33:20-22 (emphasis added).

Thus, WO '421 disclosed the elements of claim 1 reciting “[a] method for treating type 2 diabetes, comprising administering semaglutide ... to a subject in need thereof.”

WO '421 discloses that, for the treatment of type 2 diabetes, “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” (WO '421 at 43:13.) To the extent that WO '421 is deemed not to have expressly disclosed a 1.0 mg dose of semaglutide as a treatment, that dose would have been obvious to a POSA in view of the prior art.

A POSA would have been motivated to optimize the dose of semaglutide used once weekly to treat diabetes, a routine process, and it would have been obvious to a POSA to reach a dose of 1.0 mg. A POSA would have known from WO '421 that the optimized dose to be used in a once weekly treatment with semaglutide would fall in the range of 0.1-1.6 mg. WO '421 at 35:23-36:5, 43:13. In particular, a POSA would have known that patients desire fewer injections, as compared to the prior art liraglutide and exenatide treatments, which required daily and twice daily injections, respectively. A POSA also would have known from the prior art that semaglutide was an option that would be provided as a once weekly injection, a significant improvement in the eyes of patients, especially those experiencing needle phobia, and an important improvement to a POSA. *See, e.g.*, WO '537 at 1:26-33 (“Many diabetes patients particularly in the type 2 diabetes segment

are subject to so-called ‘needle-phobia’, i.e. a substantial fear of injecting themselves. In the type 2 diabetes segment most patients are treated with oral hypoglycaemic agents, and since GLP-1 compounds are expected to be the first injectable product these patients will be administered, the fear of injections may become a serious obstacle for the widespread use of the clinically very promising GLP-1 compounds. Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile.”). Given that semaglutide was already in the prior art, it would have been obvious to a POSA to further optimize the dose of semaglutide for the treatment of type 2 diabetes. Moreover, as detailed below, a significant amount of information was already in the prior art directing a POSA to the right dose.

First, a POSA would have been generally motivated to optimize the prior art dosing range of semaglutide by a desire to select the optimal treatment dose, yielding a treatment with the best benefits for patients while providing minimal side effects, which is consistent with general principles of dose selection and drug optimization (moving upward to the greatest treatment effect without incurring dose-limiting toxicities or side effects, such as nausea and vomiting).

As described above, a POSA would have understood that WO ’421’s disclosure of a dosing range from 0.1-1.6 mg for semaglutide was ultimately the disclosure of, at most, 16 possible dosing choices. However, even within the range of 16 possible doses, a POSA would have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of WO ’421’s disclosed range, as also described here. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), which shares an amino acid backbone with semaglutide, was approved in January 2010 in doses of 0.6, 1.2, and 1.8 mg. A POSA would also have known from the Victoza label (*see, e.g.*, label approved

January 2010) that Victoza's 1.2 mg dose was the targeted dose for long-term therapy, with the 1.8 mg dose used only "[i]f the 1.2 mg dose does not result in acceptable glycemic control." And, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg ("1.6 mg with titration"), see NCT00696657, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, see NCT00851773.

Further, from the prior art (e.g., from WO '421, NCT00696657, and/or NCT00851773), a POSA would have expected that, by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to use in that method, the doses disclosed in the prior art would function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work for treating type 2 diabetes.

Additionally, a POSA would have been motivated to try the 1.0 mg dose in the dose range disclosed by WO '421. A POSA would have known from WO '421 that the range of potential doses of semaglutide was 0.1-1.6 mg. WO '421 at 35:23-36:5, 43:13. And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options to try for administration to patients for the treatment of type 2 diabetes.

Thus, a POSA would have been motivated to optimize the dose within the known range of 0.1 mg to 1.6 mg of semaglutide disclosed in WO '421, and separately, would have been specifically motivated to try a 1.0 mg dose of semaglutide, once weekly.

- ii. A skilled artisan would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide

A POSA would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide. A POSA would have known from the prior art that liraglutide and semaglutide shared the same amino acid backbone (i.e., the portion of the molecule that renders it effective to bind the GLP receptor), and therefore would have reasonably expected them to behave similarly as GLP-1 receptor agonists. A POSA also would have known that there were several other GLP-1-related compounds being studied in both human and preclinical trials, each of which was known to be effective to reduce one or more of HbA_{1c} levels, body weight, and blood glucose concentrations, while avoiding the complication of hypoglycemia. *See, e.g.*, Lovshin 2009 at 263-66 (identifying, in addition to liraglutide: exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC1134, LY2199265, and LY2428757, several of which were once weekly formulations). A POSA would have reasonably expected semaglutide to behave in a generally consistent way as a GLP-1 receptor agonist, given the similarity in structure and pharmacology among the several compounds. *See, e.g.*, Knudsen 2004 at 4130, Fig. 3 (showing conserved important GLP-1 residues); *id.* Figs. 1 and 2 (GLP-1 and liraglutide sequences); '462 patent at 9:43-44 (citing WO '537 at 47:4-22 (Example 4) for semaglutide sequence).

On a related note, a POSA also would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* NCT000851773.²² While the results of those clinical trials were not yet available as of the priority date, the fact that they were being tested in human clinical trials was telling. A POSA would have known that for human clinical trials to be performed, a significant

²² <https://clinicaltrials.gov/study/NCT00851773?tab=history&a=6>

body of data related to the drug at issue would have already been collected. Moreover, a POSA would have understood that under basic clinical trial design principles, the upper end of the chosen doses would be expected to function as intended as they reached the plateau of the drug's dose-response curve, and the bottom doses were intended or expected to be suboptimal, even if some treatment effect may be apparent across the whole (or nearly whole) dose range. *See, e.g.,* Seino²³ at 164 (dose-response curve for HbA1c response versus liraglutide dose, showing suboptimal effects for the lower doses).

A POSA therefore would have optimized the known weekly dosing range for semaglutide, 0.1 mg to 1.6 mg. And separately and relatedly, would have had a reasonable expectation of success treating type 2 diabetes with a 1.0 mg weekly dose of semaglutide. Thus, claim 1 of the '462 patent would have been obvious to a POSA in view of WO '421.

b. Claim 3

Claim 2 of the '462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.” Claim 3 of the '462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”²⁴

WO '421's specification disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because WO '421 disclosed that “[s]emaglutide is

²³ Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 *Diabetes Resch. & Clinical Practice* 161 (2008).

²⁴ Claim 3 actually recites, “[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection.” Ex. 1001 ('462 patent) at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. WO ’421 at 35:23-36:5, 43:13.

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. Knudsen at 170:25-29; *see also* WO ’421 at 64:27-31 (claim 17 reciting “[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,*” which the specification instructs would have been accomplished by “subcutaneous injection” (emphasis added)). Therefore, a POSA would have understood that the “subcutaneous injection” disclosed in WO ’421 is a type of parenteral administration.

Therefore, WO ’421 disclosed the subject matter of claim 2 of the ’462 patent.

WO ’421 disclosed the subject matter of claim 3 for all the same reasons described with respect to claims 1 and 2, and further because WO ’421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. WO ’421 at 35:23-36:5, 43:13; *see also* WO ’421 at 64:27-31 (claim 17 reciting “[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,” which the specification instructs would have been accomplished by “subcutaneous injection” (emphasis added)).

Therefore, WO '421 disclosed the subject matter of claim 3 of the '462 patent, and claim 3 would have been obvious over WO421.

Thus, claims 1 and 3 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent.

c. *Claims 4, 5, and 7*

Claims 4, 5, and 7 of the '462 patent recite a method for treating type 2 diabetes, comprising once-weekly administration of 1.0 mg of semaglutide with the following properties and excipients: (1) as an isotonic aqueous solution for subcutaneous injection; (2) with propylene glycol and phenol; (3) with a phosphate buffer; and/or (4) with a pH in the range of 7.0-9.0, or at a pH of 7.4.

As of the '462 patent's priority date, a POSA would have known that the Victoza label specified the components of the liraglutide formulation. In particular, a POSA would have known that the label stated that Victoza was a solution for subcutaneous injection that included disodium phosphate dihydrate, propylene glycol, phenol and water. A POSAs also would have known that the liraglutide peptide and semaglutide peptide were very similar, as discussed above.

- i. A POSA would have been motivated to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection with a reasonable expectation of success

As noted above, Victoza® was formulated as an aqueous solution, providing motivation and a reasonable expectation of success.

This motivation and reasonable expectation of success driven by the prior art Victoza® formulation would have been informed by the wealth of the prior art within a POSAs knowledge. In particular, a POSA would have understood that parenteral dosage forms had several advantages

in treating patients over non-parenteral formulations. *See, e.g.*, Remington²⁵ at 780-81. For example, unlike oral drugs, parenteral dosage forms avoid passing through the digestive tract before being absorbed into the blood, which provided for rapid distribution throughout the body that can result in earlier onset of therapeutic effects. Remington at 780-81; Modern Pharmaceutics²⁶ at 441-444. And subcutaneous injections allow for prolonged absorption thereby increasing the duration of effect, unlike intravenous injections, which can result in poor distribution profiles and rapid clearance. Remington at 780-81; *see also* U.S. Patent No. 6,284,727 at 1:38-54, 17:8-11 (disclosed the use of GLP-1 derivatives, containing various mutations on GLP-1 (7-37) and/or chemical substituents, in parenteral formulations for subcutaneous, intramuscular, or transdermal administration). A POSA would have recognized that this was particularly beneficial for peptide-based drugs, like semaglutide, because it allowed the peptides to avoid degradation by gastric acid and potential elimination of therapeutic activity. *See, e.g.*, Remington at 780-81; NCT00696657 (clinical trial of subcutaneous dosing of semaglutide, once weekly, at doses of 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively).

Further, parenteral dosages had the benefit of avoiding hepatic metabolism and clearance of drug molecules from the portal venous blood, thereby maximizing the amount of drug that reaches the blood. Remington at 781. Moreover, subcutaneous injections are convenient, allowing for patient self-administration. *Id.*

It was also well-known as of the priority date that GLP-1 compounds had problems with solubility and stability. *See, e.g.*, WO2000037098 at 1-2. Therefore, a POSA would have

²⁵ REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000).

²⁶ Boylan, *Parenteral Products*, in MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996).

optimized GLP-1 compound formulations to provide formulations with improved solubility and stability. *See, e.g.*, Knudsen at 5:13-15; WO2000037098 at 3 (“In order to overcome the problems of chemical and physical stability of GLP-1 formulations, the present inventors have developed a shelf-stable formulation of GLP-1.”); U.S. Patent No. 7,022,674 at 5:39-43 (“The discoveries described . . . have been combined to provide novel preparations of polypeptide compositions for parenteral administration comprising glycerin that have improved chemical stability compared to polypeptide compositions previously known.”).

A POSA would have been aware that vehicles provide a liquid carrier for the drug in parenteral formulations and are necessary for most parenteral delivery routes. Remington at 783-85. Vehicles may be composed of solvents, such as water; organic liquids (like propylene glycol, glycerin, ethanol or sesame oil); or combinations of those ingredients. *Id.* Water-based vehicles are preferred due to the high solubility of polar drugs, including certain peptides, in water and the safety of aqueous vehicles. *Id.*; Modern Pharmaceutics at 457; *see also* U.S. Patent No. 5,164,366 at 7:64-8:5 (describing insulin preparations containing a pharmaceutically acceptable salt in an aqueous solution or suspension, preferably at a neutral pH, whereby “[t]he aqueous medium is made isotonic, for example with sodium chloride, sodium acetate or glycerol”).

Other factors that a POSA would have considered important to the design of a parenteral formulation include: osmolarity, pH, buffering capacity, avoiding particulates, biocompatibility of the vehicle, sterility, and choice of excipients. Remington at 780-81; Modern Pharmaceutics at 477-79.

As to the claims, WO '421 disclosed “[m]ethods 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 administration of a GLP-1 receptor agonist (e.g.

exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO ’421 at 1:4-7. WO ’421 further 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 33:20-22 (emphasis added).

Additionally, the ’833 patent disclosed that “[t]he inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known.” ’833 patent at 1:30-31. A POSA would have known that semaglutide is a peptide. *See* WO ’537 at 47:5-9 (describing semaglutide as a “peptide” and disclosing its amino acid sequence).

Accordingly, in view of WO ’421 and the ’833 patent, a POSA would have been motivated to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection with a reasonable expectation of success.

The POSA’s background knowledge from the prior art would have provided additional motivation and added to the reasonable expectation of success. A POSA would have understood from the prior art that parenteral dosage forms had several advantages in treating patients over non-parenteral formulations. For example, unlike oral drugs, parenteral dosage forms avoid passing through the digestive tract before being absorbed into the blood, which provided for rapid distribution throughout the body that can result in earlier onset of therapeutic effects. *See, e.g.,* REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000); Boylan, *Parenteral Products*, in MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996). And subcutaneous injections allow for prolonged absorption thereby increasing the duration of effect, unlike intravenous injections, which can result in poor distribution profiles and rapid clearance. Remington. A POSA would have recognized that this was particularly beneficial for peptide-based drugs, like semaglutide, because it allowed the peptides to avoid degradation by

gastric acid and potential elimination of therapeutic activity. Remington; NCT00696657 (clinical trial of subcutaneous dosing of semaglutide, once weekly, at doses of 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively).

Moreover, parenteral dosages had the benefit of avoiding hepatic metabolism and clearance of drug molecules from the portal venous blood, thereby maximizing the amount of drug that reaches the blood. Remington. Moreover, subcutaneous injections are convenient, allowing for patient self-administration. *Id.*

It was also well-known to a POSA as of the priority date that GLP-1 compounds had problems with solubility and stability. *See, e.g.*, WO0037098 at 2-3. Therefore, POSAs sought to optimise GLP-1 compound formulations to provide improved soluble and stable formulations. *See id.* at 6 (“In order to overcome the problems of chemical and physical stability of GLP-1 formulations, the present inventors have developed a shelf-stable formulation of GLP-1.”).

A POSA would have been aware that vehicles provide a liquid carrier for the drug in parenteral formulations and are necessary for most parenteral delivery routes. Remington. Vehicles may be composed of solvents, such as water; organic liquids (like propylene glycol, glycerin, ethanol or sesame oil); or combinations of those ingredients. *Id.* Water-based vehicles are preferred due to the high solubility of polar drugs, including certain peptides, in water and the safety of aqueous vehicles. *Id.*; *see also* Modern Pharmaceuticals.

Other factors that POSAs would consider important to the design of a parenteral formulation include: osmolarity, pH, buffering capacity, avoiding particulates, biocompatibility of the vehicle, sterility, and choice of excipients. Remington; Modern Pharmaceuticals.

- ii. A POSA would have been motivated to formulate semaglutide with propylene glycol and phenol with a reasonable expectation of success

A POSA would have known that the Victoza® formulation included propylene glycol and phenol, again providing a POSA with motivation and a reasonable expectation of success of using the same with semaglutide, especially in light of a POSA's knowledge of other background prior art related to such formulations.

When formulating a drug product, a POSA would have known to maintain the chemical and physical stability of peptide formulations, so the drug remains safe and effective over time in view of various environmental factors, such as temperature and pH. Thus, excipients, such as buffers, isotonicity agents, and others, were important considerations in designing peptide formulations. For example, addition of an excipient known to provide a stabilizing effect to a peptide drug, such as propylene glycol and phenol, could stabilize a peptide drug formulation.

Further, because excipients can have profound effects on the performance of a drug, a POSA would have understood that it was important that parenteral preparations should be “of the very best quality and provide the maximum safety for the patient.” Remington at 781. Further, regulatory agencies like FDA require the role and amount of each excipient to be justified, require the developer to ensure there are no incompatibilities between the excipients and the active drug, and require ongoing quality control of each excipient during manufacturing. Modern Pharmaceutics at 452; Remington at 781-82.

Thus, a POSA would have understood the importance of keeping the peptide formulations as simple as possible and, if possible, to use excipients that have previously been used in FDA-approved formulations. See, e.g., approved Victoza label (Victoza was available as a “[s]olution for subcutaneous injection” in a “pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg” with the following inactive ingredients: “disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection”). Consequently, A POSA knew

that it would be preferable to minimize the number of excipients used in a parenteral dosage form. Modern Pharmaceuticals at 452.

WO '421 disclosed that injectable formulations of GLP-1 receptor agonists “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.” WO '421 at 39:23-26.

The '833 patent claimed “[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.” '833 patent at 22:48-54 (claim 1).

WO '421 disclosed the use of propylene glycol (WO '421 at 37:35) and the '833 patent disclosed “[a] pharmaceutical formulation comprising ... propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.” '833 patent at 22:48-54 (claim 1). The '833 patent further disclosed the use of propylene glycol as an isotonicity agent in aqueous solutions containing GLP-1 agonists. *See id.* (the use of propylene glycol as an isotonicity agent); *id.* at 2:35-40 (same).

The '833 patent also disclosed that “[t]he use of a preservative in pharmaceutical compositions is well-known to the skilled person,” *id.* at 11:6-9, and that “phenol (5.0 or 5.5 mg/ml)” is a preservative. *Id.* at 20:13-15. The '833 patent further disclosed that “[i]n a preferred embodiment of the invention the preservative is phenol or m-cresol.” *Id.* at 10:65-67.

The '833 patent further disclosed that propylene glycol at certain concentrations in peptide formulations reduced deposits and clogging of injection devices. *Id.* at 1:53-57; *id.* at 13:43-45 (“the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular.”), *id.* at 2:58-62 (“[t]he present invention further relates to a method for reducing the clogging of injection devices by a peptide formulation, where the method comprises replacing the isotonicity agent previously utilized in said formulation with propylene glycol at a concentration of between 1-100 mg/ml.”).

Accordingly, in view of WO '421 and the '833 patent, a POSA would have been motivated to formulate semaglutide with propylene glycol and phenol with a reasonable expectation of success.

- iii. A POSA would have been motivated to formulate semaglutide with a phosphate buffer with a reasonable expectation of success

A POSA would have known that the Victoza® formulation also included the phosphate buffer, sodium dihydrogen phosphate, again providing POSAs motivation with a reasonable expectation of success of using the same with semaglutide, especially in light of a POSA's knowledge of other background prior art related to such formulations.

A POSA would have been aware of the importance of buffers to maintain the pH of the formulation. A buffer is a solution that resists change in pH when an acid or alkali is added or when the solution is diluted. Because parenteral formulations are designed to be injected directly into a patient, use of the buffer is particularly important to (1) preserve a physiological pH, which is about pH 7.4, to not cause tissue damage and pain at the site of injection, and (2) maintain stability and solubility of the drug for its intended shelf-life. *See, e.g.,* Modern Pharmaceutics at 456, 473; Remington at 705; *see also* U.S. Patent No. 6,458,924 at 153:46-56, 201:11-204:34

(providing formulations including GLP-1 derivatives, an isotonic agent, a buffer, and a preservative).

A POSA would also have been aware of using a phosphate as the buffer, such as sodium dihydrogen phosphate. WO '136 taught that the buffer may be selected from “sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, [or] tris(hydroxymethyl)-aminomethan.” WO2003002136 at 17:27-30; *see also* U.S. Patent No. 7,022,674 at 33:27-43 (disclosing a 10 mL solution of the insulin analog derivative that contains 3.7 mg/mL of myristoyl- ϵ -Lys(B29)-des(B30)-human insulin, 16 mg/mL glycerin, 7mM sodium phosphate, and 3.2 mg/mL m-cresol at a pH of about 7.9); *id.* at 34:7-18 (disclosing a 1 mg/mL human leptin solution containing 16 mg/mL glycerin, 7 mM sodium phosphate, 3 mg/mL m-cresol and the pH of 8.0). WO2003002136 further described “glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, [and] sodium phosphate” as “preferred.” 17:30-33.

WO '421 disclosed that injectable formulations of GLP-1 receptor agonists “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.” WO '421 at 39:23-26.

The '833 patent claimed “[a] pharmaceutical formulation comprising at least one GLP-1 agonist, a disodium phosphate dihydrate buffer and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to about 10.0.” '833 patent at 22:48-54 (claim 1). A POSA would have known from this that disodium phosphate dihydrate is a phosphate buffer, as claimed in claims 4, 8, and 9 of the '462 patent.

Examples 1-6 of the '833 patent (each exemplary formulation) disclosed the use of a phosphate buffer at a pH within the range of 7.0-9.0. *Id.* at 15:62-22:21.

The '833 patent further disclosed a “preferred” buffer of “glycylglycine, ... sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate ... or mixtures thereof,” as well as other suitable buffers: “the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, or mixtures thereof.” *Id.* at 10:47-57.

The '833 patent's examples disclosed a liraglutide composition with a pH of 7.40 containing sodium dihydrogen phosphate (Example 4) and a composition with a pH of 7.4 (Example 5). *Id.* at 20:20-67.

Accordingly, in view of WO '421 considering the '833 patent, a POSA would have been motivated to formulate semaglutide with a phosphate buffer with a reasonable expectation of success.

- iv. A POSA would have been motivated to formulate semaglutide with a pH in the range of 7.0-9.0, or at a pH of 7.4, with a reasonable expectation of success

As of the priority date of the '462 patent, a POSA would have known that specific parameters, such as pH and tonicity, must be considered when developing a parenteral formulation to minimize potential adverse effects, including tissue damage and injection pain. Modern Pharmaceuticals at 477-79. Because parenteral dosage forms are often intended for multiple dosing, a POSA would have been aware that antimicrobial excipients may be necessary in the formulation. Remington at 785. A POSA would also have recognized the importance of maintaining the

physical and chemical stability of the drug formulation to minimize the risk of impurities during manufacturing, storage, and handling. *Id.*; Modern Pharmaceuticals at 441-44.

A POSA would also have been aware that extreme values of pH, such as 2.3 and 11, may result in tissue injury and cell death. Modern Pharmaceuticals at 477-79. Thus, a POSA would have understood that a parenteral formulation should have a pH that is safe for the intended injection site and the intended volume. *See, e.g.*, Remington at 781; Modern Pharmaceuticals at 477-79; *see also, e.g.*, U.S. Patent No. 7,022,674 at 33:27-43 (disclosing a 10 mL solution of an insulin analog derivative that contains 3.7 mg/mL of myristoyl- ϵ -Lys(B29)-des(B30)-human insulin, 16 mg/mL glycerin, 7mM sodium phosphate, and 3.2 mg/mL m-cresol at a pH of about 7.9).

WO '421 disclosed that injectable formulations of GLP-1 receptor agonists “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.” WO '421 at 39:23-26.

The '833 patent claimed “[a] pharmaceutical formulation comprising at least one peptide and propylene glycol, wherein said propylene glycol is present in said formulation in a final concentration of from about 1 mg/ml to about 100 mg/ml and wherein said formulation has a pH of from about 7.0 to 10.0.” '833 patent at 22:48-54 (claim 1).

A dependent claim in the '833 patent claimed “[t]he formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.” *Id.* at 22:66-67. Examples 1-6 of the '833 patent (each exemplary formulation) disclosed the use of a phosphate buffer at a pH within the range of 7.0-9.0. *Id.* at 15:62-22:21.

Example 3 of the '833 patent disclosed using a formulation with a pH of “7.40, 7.70, 7.90, or 8.15.” *Id.* at 20:19. The '833 patent's examples disclosed a liraglutide composition with a pH

of 7.40 containing sodium dihydrogen phosphate (Example 4) and a composition with a pH of 7.4 (Example 5). *Id.* at 20:21-67.

The '833 patent disclosed “[a] pharmaceutical formulation comprising ... propylene glycol, . . . and wherein said formulation has a pH of from about 7.0 to about 10.0.” *Id.* at 22:48-54 (claim 1).

Accordingly, in view of WO '421 and the '833 patent, a POSA would have been motivated to formulate semaglutide with a pH in the range of 7.0-9.0, or at a pH of 7.4, with a reasonable expectation of success.

v. The dependent limitations of claim 4 would have been obvious

Claim 4 depends from claim 1 and recites the additional limitation “wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.” '462 patent at 35:49-52.

As detailed above, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 4.

A POSA would have known from WO '421 and the '833 patent that administering semaglutide by subcutaneous injection in the form of an isotonic aqueous solution would (1) allow for prolonged absorption thereby increasing the duration of effect; (2) avoid poor distribution profiles and rapid clearance; and (3) allow the peptides to avoid degradation by gastric acid and potential elimination of therapeutic activity. *See, e.g.*, WO '421 at 35:23-36:5, 43:13 (disclosing that semaglutide is administered “by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes); '833 patent at 1:30-31 (disclosing that “[t]he inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known”).

These references also taught a POSA that the addition of a phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4, to not cause tissue damage and pain at the site of injection, and (2) maintain stability and solubility of the drug for its intended shelf-life. *See, e.g.*, WO '421 at 39:23-26 (using known additives in GLP-1 receptor agonist formulation “for aiding solubility or for preservation” to “obtain injectable solutions”); '833 patent at 15:62-22:21 (in aqueous solutions containing GLP-1 agonists, using disodium phosphate dihydrate as a “preferred” buffer).

These references further taught a POSA to formulate semaglutide with a pH in the range of 7.0-9.0 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, WO '421 at 39:23-26 (using known additives in GLP-1 receptor agonist formulation “for aiding solubility or for preservation” to “obtain injectable solutions”); '833 patent at 15:62-22:21 (disclosing GLP-1 agonist formulations with a pH within the range of 7.0-9.0, and specifically at 7.40).

Accordingly, claim 4 of the '462 patent would have been obvious over WO '421 in view of the '833 patent.

- vi. The dependent limitations of claim 5 would have been obvious

Claim 5 depends from claim 4 and recites the additional limitation “wherein the solution further comprises propylene glycol and phenol.” '462 patent at 35:53-54.

A POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 5.

WO '421 and the '833 patent taught a POSA that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, WO '421 at 37:35, 39:23-26 (using propylene glycol as an excipient in GLP-1 receptor agonist formulation “for aiding

solubility or for preservation” to “obtain injectable solutions”); ’833 patent at 22:48-54 (claim 1), 23:3-4 (claim 8), 20:14-16 (in aqueous solutions containing GLP-1 agonists, using propylene glycol as an isotonicity agent and phenol as a “preferred” preservative).

Accordingly, claim 5 of the ’462 patent would have been obvious over WO ’421 in view of the ’833 patent.

- vii. The dependent limitations of claim 7 would have been obvious

Claim 6 depends from claim 4 and recites the additional limitation “wherein the pH is 7.4.” ’462 patent at 36:40-41. Claim 7 depends from claim 6 and recites the additional limitation “wherein the solution further comprises propylene glycol and phenol.” ’462 patent at 35:42-43.

A POSA would have been motivated to formulate, with a reasonable expectation of success, the formulation limitation recited in claim 6.

WO ’421 and the ’833 patent taught a POSA to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, WO ’421 at 39:23-26 (using known additives in GLP-1 receptor agonist formulation “for aiding solubility or for preservation” to “obtain injectable solutions”); ’833 patent at 15:62-22:21 (disclosing GLP-1 agonist formulations with a pH within the range of 7.0-9.0, and specifically at 7.40).

Regarding the additional limitation recited in claim 7, WO ’421 and the ’833 patent taught a POSA that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, WO ’421 at 37:35, 39:23-26 (using propylene glycol as an excipient in GLP-1 receptor agonist formulation “for aiding solubility or for preservation” to “obtain injectable solutions”); ’833 patent at 22:48-54 (claim 1), 23:3-4 (claim 8), 20:14-16 (in aqueous solutions containing GLP-1 agonists, using propylene glycol as an isotonicity agent and phenol as a “preferred” preservative).

Accordingly, claim 7 of the '462 patent would have been obvious in view of WO '421 in view of the '833 patent.^r

3. Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin 2009

d. Claim 1

Claim 1 of the '462 patent recites “[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.”

- i. A skilled artisan would have been motivated to pursue the method recited in claim 1

The disclosures of WO '537 are described above.

WO '537²⁷ disclosed using modified GLP-1 peptides to treat type 2 diabetes, i.e., that the composition “may be administered to a patient in need of such treatment.” WO '537 at 23:24-29, 33:32-33. Example 4 of WO '537 discussed semaglutide, *id.* at 48:4-22, and a patient with type 2 diabetes in need of treatment with a GLP-1 peptide, which improves glycemic control, *id.* at 23:24-26.

WO '537 also disclosed that the compounds it described could be used to prepare a medicament for delaying, treating, or preventing disease progression for type 2 diabetes. *Id.* at 39:3-4. WO '537 disclosed that semaglutide formulations of a variety of concentrations could be prepared, such as from 0.1 mg/mL to 25 mg/mL. *Id.* at 25:11-13. And WO '537 disclosed once weekly administration of GLP-1 peptides, including semaglutide: “One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.” *Id.* at 60:24-25.

²⁷ WO537 shares a specification with U.S. Patent Application Publication No. 2009/0156478 and U.S. Patent No. 8,129,343.

WO '537 also described how to screen once weekly GLP-1 analogs for activity in a mouse model:

Pharmacokinetic screening of GLP-1 analogues for identification of suitable once weekly candidates were performed on candidates that according to the project screenings plan were shown to be sufficiently potent with respect to glucose lowering potential in a diabetic mouse model (db/db mice) and subsequently had a time of duration of 48 hours or more in the db/db mouse model.

Id. at 60:24-32; see also *id.* at 60:34-61:29.

Thus, WO '537 disclosed the elements of claim 1 reciting “[a] method for treating type 2 diabetes, comprising administering semaglutide once weekly ... to a subject in need thereof.”

Lovshin 2009 disclosed, further, that NN9535 (i.e., semaglutide, as a POSA would have been known) was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin 2009 at 263, Table 1. It would have been obvious to a POSA to optimize the dose of semaglutide to a dose of 1.0 mg and/or the 1.0 mg dose would have been obvious to try in that disclosed dose range, and the POSA would have been motivated to do so by a desire to select the optimal treatment dose, targeting the best balance between treatment benefit and adverse events.

A POSA would have known from Lovshin 2009 that the optimized dose to be used in a once weekly treatment with semaglutide would fall in the range of 0.1-1.6 mg. Lovshin 2009 at 263, Table 1 (“0.1-1.6 mg once weekly”). As detailed below, a significant amount of information was already in the prior art directing POSAs to the right dose.

First, a POSA would have been generally motivated to optimize the prior art dosing range of semaglutide by a desire to select the optimal treatment dose, yielding a treatment with the best benefits for patients while providing minimal side effects, which is consistent with general

principles of dose selection and drug optimization (moving upward to the greatest treatment effect without yielding dose-limiting toxicities or side effects, such as nausea and vomiting).

As detailed above, Lovshin 2009's disclosure of a dosing range from 0.1 to 1.6 mg for semaglutide was ultimately the disclosure of, at most, 16 possible choices. However, even within the range of 16 possible doses, a POSA would have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of Lovshin 2009's disclosed range, as described below. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), which shares an amino acid backbone with semaglutide, was approved in January 2010 in doses of 0.6, 1.2, and 1.8 mg. A POSA would also have known that Victoza's 1.2 mg dose was the targeted dose for long-term therapy, with the 1.8 mg dose used only if the 1.2 mg dose does not result in acceptable glycemic control. And, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* NCT000851773.

Further, from one or more of these disclosures (i.e., from WO '421, Lovshin 2009, NCT00696657, and/or NCT00851773), a POSA would have expected that, by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to use in that method, the doses disclosed in the prior art would function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work for treating type 2 diabetes.

In addition, a POSA would have been motivated to try the 1.0 mg dose in the dose range disclosed by Lovshin 2009. A POSA would have known from Lovshin 2009 that the range of

potential doses of semaglutide was 0.1-1.6 mg. Lovshin 2009 at 263, Table 1 (“0.1-1.6 mg once weekly”). And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options to try for administration to patients for the treatment of type 2 diabetes, as described above.

Thus, a POSA would have been motivated to optimize the known range of 0.1 mg to 1.6 mg of semaglutide disclosed in Lovshin 2009, and separately, would have been specifically motivated to pursue a 1.0 mg dose of semaglutide, once weekly.

- ii. A skilled artisan would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide

A POSA would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide. A POSA would have known from the prior art that liraglutide and semaglutide shared the same amino acid backbone (i.e., the portion of the molecule that renders it effective to bind the GLP receptor), and therefore would have reasonably expected them to behave in similar fashion as GLP-1 receptor agonists. A POSA also would have known that liraglutide and semaglutide shared amino acids known from earlier work and available in the prior art, Knudsen 2004²⁸ at 3, Fig. 3, to be essential for binding:

Knudsen 2004 Fig. 3 essential residue	Present in liraglutide?	Present in semaglutide?
His7	Yes	Yes
Gly10	Yes	Yes
Phe12	Yes	Yes
Thr13	Yes	Yes
Asp15	Yes	Yes
Phe28	Yes	Yes
Ile29	Yes	Yes

²⁸ Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 JOURNAL OF MEDICINAL CHEMISTRY 4128 (2004).

Knudsen 2004 Fig. 3 essential residue	Present in liraglutide?	Present in semaglutide?
Val33	Yes	Yes

See Knudsen 2004 at 4130, Fig. 3; *Id.*, Fig. 2 (liraglutide sequence); '462 patent at 9:43-44 (citing WO '537 at 48:4-22 (Example 4) for semaglutide sequence).

As further support, a POSA would have known that there were several other GLP-1-related compounds being studied in both human and preclinical trials, each of which was known to be effective to reduce blood glucose, HbA_{1c} levels, and body weight, while avoiding the complication of hypoglycemia. See Lovshin 2009 at 263-66 (identifying, in addition to liraglutide, exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC-1134-PC, LY2189265, and LY2428757, several of which were once weekly formulations). A POSA would have reasonably expected semaglutide to provide the same benefits, given that the several compounds all belonged to the same class of GLP-1 receptor agonists. Lovshin 2009 at 2-5; *see also* Knudsen 2004 at 4130, Figs. 1 and 2 (GLP-1 and liraglutide sequences); '462 patent at 9:43-44 (citing WO '537 at 48:4-22 (semaglutide sequence)).

Related, as described above, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* NCT000851773. While the results of those clinical trials were not yet available as of the priority date, the fact that they were being tested in human clinical trials was telling. A POSA would have known that for human clinical trials to be performed, a significant body of data related to the drug at issue would have already been collected. Moreover, a POSA would have understood that under basic clinical trial design principles, the upper end of the chosen doses would be expected to function as intended, and the bottom doses were intended or expected

to be suboptimal, even if they could still have some amount of treatment effect. *See, e.g.*, Seino at 164 (dose-response curve for HbA1c response versus liraglutide dose, showing greater treatment effect with the larger doses).

A POSA therefore would have optimized the known weekly dosing range for semaglutide, 0.1 mg to 1.6 mg. And separately and relatedly, a POSA would have had a reasonable expectation of success in treating type 2 diabetes with a 1.0 mg weekly dose of semaglutide. Thus, claim 1 of the '462 patent would have been obvious to a POSA over WO '537 in view of Lovshin 2009.

e. Claim 3

Claim 2 of the '462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.” Claim 3 of the '462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”²⁹

WO '537 disclosed that “[p]arenteral administration [of semaglutide] may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.” WO '537 at 34:15-16; *see also id.* at 34:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

Thus, in addition to rendering obvious the subject matter of claim 1, in conjunction with Lovshin 2009, WO '537 further disclosed claim 2's requirement that “semaglutide is administered by parenteral administration.”

Regarding the subject matter of claim 3, WO '537 disclosed that “[p]arenteral administration [of semaglutide] may be performed by subcutaneous, intramuscular, intraperitoneal

²⁹ Claim 3 actually recites, “[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection.” Ex. 1001 ('462 patent) at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

or intravenous injection by means of a syringe, optionally a pen-like syringe,” and a POSA would have understood that the injection was of a solution. WO ’537 at 34:15-16; *see also id.* at 34:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

Thus, in addition to rendering obvious the subject matter of claim 1, in conjunction with Lovshin 2009, WO ’537 further disclosed claim 3’s requirement that the parenteral administration occurs “by subcutaneous injection.” Therefore, claim 3 would have been obvious over WO ’537 in view of Lovshin 2009.

f. Claims 4, 5, and 7

Claims 4, 5, and 7 of the ’462 patent recite a method for treating type 2 diabetes, comprising once-weekly administration of 1.0 mg of semaglutide with the following properties and excipients: (1) as an isotonic aqueous solution for subcutaneous injection; (2) with propylene glycol and phenol; (3) with a phosphate buffer; and/or (4) with a pH in the range of 7.0-9.0, or at a pH of 7.4.

As of the ’462 patent’s priority date, a POSA would have known that the Victoza label specified the components of the liraglutide formulation. In particular, a POSA would have known that the label stated that Victoza was a solution for subcutaneous injection that included disodium phosphate dihydrate, propylene glycol, phenol and water. A POSAs also would have known that the liraglutide peptide and semaglutide peptide were very similar, as discussed above.

- i. A POSA would have been motivated to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection with a reasonable expectation of success

As noted above, Victoza® was formulated as an aqueous solution, providing motivation and a reasonable expectation of success, especially in view of the abundant prior art on this issue.

See Section IX.B.2.c.i.

WO '537 disclosed using modified GLP-1 peptides to treat type 2 diabetes, i.e., that the composition “may be administered to a patient in need of such treatment.” WO '537 at 22:24-29, 32:32-33. Example 4 of WO '537 discussed semaglutide, *id.* at 47:4-22, and a patient with type 2 diabetes in need of treatment with a GLP-1 peptide, which improves glycemic control, *id.* at 22:24-26.

WO '537 also disclosed that the GLP-1 peptides could be used to prepare a medicament for delaying, treating, or preventing disease progression for type 2 diabetes. *Id.* at 38:3-4. WO '537 disclosed that semaglutide formulations of a variety of concentrations could be prepared, such as from 0.1 mg/mL to 25 mg/mL. *Id.* at 24:11-13. And WO '537 disclosed once-weekly administration of GLP-1 peptides, including semaglutide. *Id.* at 59:24-25.

WO '537 further disclosed that “[p]arenteral administration [of semaglutide] may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.” *Id.* at 34:15-16; *see also id.* at 34:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

Lovshin 2009 disclosed that NN9535 (i.e., semaglutide), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin 2009 at 263. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

Accordingly, in view of WO '537 considering Lovshin 2009, and in light of the state of the art, a POSA would have been motivated to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection with a reasonable expectation of success.

- ii. A POSA would have been motivated to formulate semaglutide with propylene glycol and phenol with a reasonable expectation of success

A POSA would have known that the Victoza® formulation included propylene glycol and phenol, again providing POSAs motivation with a reasonable expectation of success of using the same with semaglutide, especially in light of the abundant prior art. *See* Section IX.B.2.c.ii.

WO '537 provided a specific example of a pharmaceutical formulation comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15. WO '537 at 63:10-15.

WO '537 further disclosed a formulation that “comprises a pharmaceutically acceptable preservative. In a further embodiment of the invention the preservative is selected from the group consisting of phenol . . .” *Id.* at 25:11-13. WO '537 also disclosed that in “an embodiment the isotonicity agent is propyleneglycol.” *Id.* at 25:34-35. Further, WO '537 provided an example of a formulation comprising semaglutide (“compound of example 4”), propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15 (i.e., within the range 7.0-9.0). *Id.* at 63:10-15; *see also* '833 patent at 19:38-20:19 (disclosing a formulation with a pH of 7.4).

Adding to WO '537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin 2009 at 263. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

Accordingly, in view of WO '537 considering Lovshin 2009, and in light of the state of the art, a POSA would have been motivated to formulate semaglutide with propylene glycol and phenol with a reasonable expectation of success.

- iii. A POSA would have been motivated to formulate semaglutide with a phosphate buffer, with a reasonable expectation of success

A POSA would have known that the Victoza® formulation also included the phosphate buffer, sodium dihydrogen phosphate, again providing POSAs motivation with a reasonable expectation of success of using the same with semaglutide. *See* Section IX.B.2.c.iii.

Further, WO '537 disclosed pharmaceutical formulations comprising GLP-1 compounds, such as semaglutide, with excipients “such as buffer, preservative, and optionally a tonicity modifier and/or a stabilizer. Thus a pharmaceutical composition is also known in the art as a pharmaceutical formulation.” WO '537 at 5:32-35.

WO '537 further disclosed a pharmaceutical formulation “in a concentration from 0.1 mg/ml to 25 mg/ml” and “a pH from 3.0 to 9.0. The formulation may further comprise a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants. In one embodiment of the invention the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water.” *Id.* at 24:11-16.

WO '537 also provided exemplary buffers for a formulation:

In a further embodiment of the invention the buffer is selected from the group consisting of sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginine, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, and tris(hydroxymethyl)-aminomethan, bicine, tricine, malic acid, succinate, maleic acid, fumaric acid, tartaric acid, aspartic acid or mixtures thereof.

Id. at 25:4-8.

Adding to WO '537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin 2009 at 263. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

Accordingly, in view of WO '537 considering Lovshin 2009, and in light of the state of the art, a POSA would have been motivated to formulate semaglutide with a phosphate buffer, with a reasonable expectation of success.

- iv. A POSA would have been motivated to formulate semaglutide with a pH in the range of 7.0-9.0, or at a pH of 7.4, with a reasonable expectation of success

A POSA as of the priority date of the '462 patent would have been motivated to formulate semaglutide with a pH in the range of 7.0-9.0, or at a pH of 7.4, with a reasonable expectation of success. See Section IX.B.2.c.iv.

WO '537 disclosed pharmaceutical formulations comprising GLP-1 compounds, such as semaglutide, with excipients “such as buffer, preservative, and optionally a tonicity modifier and/or a stabilizer. Thus a pharmaceutical composition is also known in the art as a pharmaceutical formulation.” WO '537 at 5:32-35.

WO '537 further disclosed a pharmaceutical formulation “in a concentration from 0.1 mg/ml to 25 mg/ml” and “a pH from 3.0 to 9.0. The formulation may further comprise a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants. In one embodiment of the invention the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water.” *Id.* at 24:11-16.

WO '537 provided exemplary pH ranges for a formulation:

In another embodiment of the invention the pH of the formulation is from about 7.0 to about 9.5. In another embodiment of the invention the pH of the formulation is from about 3.0 to about 7.0. In another embodiment of the invention the pH of the formulation is from about 5.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 9.0. In another embodiment of the invention the pH of the formulation is from about 7.5 to about 8.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.5. In another embodiment of the invention the pH of the formulation is from about 6.0 to about 7.0. In another embodiment the pharmaceutical formulation is from 8.0 to 8.5.

Id. at 24:30-25:2.

Adding to WO '537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin 2009 at 263. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

Accordingly, in view of WO '537, considering Lovshin 2009, and in light of the state of the art, a POSA would have been motivated to formulate semaglutide with a pH in the range of 7.0-9.0, or at a pH of 7.4, with a reasonable expectation of success.

v. The dependent limitations of claim 4 would have been obvious

Claim 4 depends from claim 1 and recites the additional limitation “wherein the semaglutide is administered in the form of an isotonic aqueous solution comprising phosphate buffer at a pH in the range of 7.0-9.0.” ’462 patent at 35:49-52.

As detailed above, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 4.

Notably, WO '537 and Lovshin 2009 taught POSAs that administering semaglutide by subcutaneous injection in the form of an isotonic aqueous solution would (1) allow for prolonged absorption thereby increasing the duration of effect; (2) avoid poor distribution profiles and rapid clearance; and (3) allow the peptides to avoid degradation by gastric acid and potential elimination of therapeutic activity. *See, e.g.*, WO '537 at 35:3-16 (disclosing that semaglutide is preferably administered subcutaneously by a pen-like syringe); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

These references also taught POSAs that the addition of a phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4, to not cause tissue damage and pain at the site of injection, and (2) maintain stability and solubility of the drug for its intended shelf-life. *See, e.g.*, WO '537 at 25:4-8 (in an aqueous GLP-1 compound formulation, such as semaglutide, using disodium phosphate dihydrate as an exemplary buffer); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

These references further taught POSAs to formulate semaglutide with a pH in the range of 7.0-9.0 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, WO '537 at 24:11-25:2 (disclosing an aqueous formulation with a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants, within pH ranges from, e.g., 7.0-9.5 and 7.5-9.0); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

Accordingly, claim 4 of the '462 patent would have been obvious in view of WO '537 considering Lovshin 2009.

- vi. The dependent limitations of claim 5 would have been obvious

Claim 5 depends from claim 4 and recites the additional limitation "wherein the solution further comprises propylene glycol and phenol." '462 patent at 35:53-54.

A POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 5.

WO '537 and Lovshin 2009 taught a POSA that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, WO '537 at 25:11-35, 63:10-15 (disclosing phenol as a preservative and propylene glycol as the isotonicity agent, and providing an example of a semaglutide formulation comprising propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

Accordingly, claim 5 of the '462 patent would have been obvious in view of WO '537 considering Lovshin 2009.

- vii. The dependent limitations of claim 7 would have been obvious

Claim 6 depends from claim 4 and recites the additional limitation “wherein the pH is 7.4.” ’462 patent at 36:40-41. Claim 7 depends from claim 6 and recites the additional limitation “wherein the solution further comprises propylene glycol and phenol.” ’462 patent at 35:42-43.

A POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 6.

WO ’537 and Lovshin 2009 taught a POSA to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, WO ’537 at 24:11-25:2 (disclosing an aqueous formulation with a buffer system, preservative(s), tonicity agent(s), chelating agent(s), stabilizers and surfactants, within pH ranges from, e.g., 7.0-9.5 and 7.5-9.0); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

Regarding the additional subject matter of claim 7, WO ’537 and Lovshin 2009 taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, WO ’537 at 25:11-35, 63:10-15 (disclosing phenol as a preservative and propylene glycol as the isotonicity agent, and providing an example of a semaglutide formulation comprising propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15); Lovshin 2009 at 263 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

Accordingly, claim 7 of the ’462 patent would have been obvious in view of WO ’537 considering Lovshin 2009.

4. Secondary Considerations

Secondary considerations do not support nonobviousness of the claims of the '462 patent. Defendants discuss below aspects of secondary considerations and reserve the right to identify other factual support for their positions as discovery proceeds in this case, and in rebuttal to any secondary considerations asserted by Plaintiffs.

Initially, Defendants note that there is not, and cannot be, any nexus between any secondary considerations asserted by Plaintiffs and the claimed method of using 1.0 mg semaglutide once weekly to treat diabetes. First, the driver of any secondary considerations related to the '462 patent is the presence of semaglutide, and the inherent characteristics it possesses due to its chemical structure and biological activity as a GLP-1 receptor agonist. But semaglutide was both known in the art in numerous other pre-priority date references and was independently patented by Novo Nordisk in the '343 and '122 patents. Thus, even beyond the fact that various aspects of secondary considerations can only be attributed to the claimed subject matter of the '343 and '122 patents, the presence of those patents prevented any other market participants or potential entrants from using semaglutide to develop and commercialize the inventions claimed in the '462 patent. Second, there can be no nexus to the claims of the '462 patent because the prior art disclosed ranges of once weekly semaglutide doses to treat diabetes and doses almost identical to the dose claimed in the '462 patent (see, e.g., NCT00696657, disclosing a dose of 0.8 mg once weekly to treat diabetes); thus, to the extent various secondary considerations may be asserted, they were provided by the doses disclosed in the prior art. Further, secondary considerations cannot have a nexus simply to using semaglutide to treat type 2 diabetes, independent of the dosing amount and frequency, because the '343 and '122 patents already disclosed using semaglutide in that method. See, e.g., '343 patent at 40:36-39 (describing the use of semaglutide “for the preparation of a medicament for the treatment or prevention of ... type 2 diabetes”), 129:4-132:36 (claiming

semaglutide and its use in “an effective amount” to treat type 2 diabetes). Thus, even before filing and issuance of the ’462 patent, with a patent on the semaglutide molecule and its use to treat diabetes, Novo Nordisk had a protected monopoly.

Regarding commercial success, there is no nexus between the sales of Ozempic asserted to support commercial success and the claim limitations, even beyond the problems noted generally above. For example, Ozempic has been approved in multiple once weekly doses: 0.25 mg, 0.5 mg, 1.0 mg, and 2.0 mg. The 1.0 mg dose is but one of these and it is, at best, just a portion of Ozempic’s sales. See *Ozempic Prescribing Information*, Ozempic (Oct. 2023), <https://www.ozempic.com/prescribing-information.html> [REDACTED] [REDACTED] [REDACTED] [REDACTED] [REDACTED]

[REDACTED] And often, when Ozempic is administered in a 1.0 mg dose it is for the treatment of obesity rather than diabetes, to the point that some in the popular press identify it as an obesity drug while touting its alleged runaway success. See A. Pawlowski, *Ozempic Before and After: 5 Women Get Real About Weight Loss, Side Effects and Cost*, Today (Aug. 14, 2023, 9:54 AM), <https://www.today.com/health/diet-fitness/ozempic-before-and-after-rcna99185> (“Ozempic isn’t approved for weight loss but that’s a famous side effect, so some doctors have been prescribing it off-label for that purpose.”); A. Adegbesan, *Weight-Loss Drugs Like Ozempic Are in Such Huge Demand that Spending on Them Will Hit \$100 Billion By 2035, Analyst Says*, Fortune (Sept. 22, 2023), <https://fortune.com/2023/09/22/obesity-drug-market-ozempic-wegovy-2035/>.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Because discovery on this issue is not closed, Defendants specifically reserve the right to supplement the facts and arguments in support of this position.

Further, there was no long-felt need for the invention and/or use of a once weekly GLP-1-agonist diabetes treatment and there was no failure of others to develop a weekly GLP-1 diabetes treatment. For example, both Trulicity and other once weekly GLP-1 receptor agonists were already in development or on the market before Ozempic. *See, e.g.*, [REDACTED]

[REDACTED] Lovshin 2009 at 263 (Table 1) (identifying once weekly GLP-1 receptor agonists); Lund³⁰ (same).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

³⁰ Lund, *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Last, there was no skepticism from the market or any POSA regarding the potential feasibility or success of a once weekly GLP-1 treatment; indeed, the prior art arguments show, above, that a POSA would have had a reasonable expectation that the claimed method would be successful. For example, [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

C. The Claims of the '462 Patent Are Invalid for Lack of Enablement, for Lack of Written Description, Lack of Utility, and/or Because They Are Indefinite

1. The claims of the '462 patent are invalid for lack of enablement

The claims of the '462 patent are invalid for lack of enablement under 35 U.S.C. § 112. The claims recite methods of treating type 2 diabetes by administering 1.0 mg of semaglutide once weekly. However, the specification provides no support for such a dosage, much less using such a dosage for the “treatment” of type 2 diabetes. Further, there is also no data (clinical trials or experimental) demonstrating the “treatment” of patients with type 2 diabetes using the recited dose. Furthermore, the specification provides no guidance as to how one would arrive at this specific dosing range. Thus, the claims fail to meet the enablement requirement of 35 U.S.C. § 112.

2. The claims of the '462 patent are invalid for lack of written description

The test for written description “is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date.” *Ariad Pharms.*, 598 F.3d at 1351. “[T]he description must ‘clearly allow persons of ordinary skill in the art to recognize that [the inventor] invented what is claimed.’” *Id.* (quoting *Vas-Cath Inc. v. Mahurkar*, 935 F.2d 1555, 1562–63 (Fed. Cir. 1991)). “[I]t is the specification itself that must demonstrate possession.” *Id.* at 1352. “[A]ctual ‘possession’ or reduction to practice outside of the specification is not enough.” *Id.*

“The disclosure of a broad range of values does not by itself provide written description support for a particular value within that range.” *Gen. Hosp. Corp. v. Sienna Biopharmaceuticals, Inc.*, 888 F.3d 1368, 1372 (Fed. Cir. 2018). “Instead, where a specification discloses a broad range of values and a value within that range is claimed, the disclosure must allow one skilled in the art to ‘immediately discern the limitation at issue in the claims.’” *Id.* In other words, “one cannot

disclose a forest in the original application, and then later pick a tree out of the forest and say here is my invention.” *Purdue Pharma L.P. v. Faulding Inc.*, 230 F.3d 1320, 1326 (Fed. Cir. 2000).

The '462 patent's specification discloses a broad range of dose values but does not show that the inventors had actual possession of the specifically claimed 1.0 mg dose. (See '462 Patent at col. 3 ll. 41-55, col. 15 ll. 16-18, col. 17 ll. 20-34.) Not a single working example is provided in the specification relating to the 1.0 mg dose. The specification instead focuses heavily on the 0.7 mg dose, which is what the initially filed claims of the '042 application were directed to. (*Id.* at col. 1 ll. 41-43, col. 1 ll. 51-54, col. 1 ll. 64-66, col. 4 ll. 7-43, col. 16 ll. 58-64, col. 20 ll. 17-27, col. 20 ll. 31-44.) Though the specification describes a clinical study testing semaglutide doses ranging from 0.1 mg through 1.6 mg, that study does not specifically describe the 1.0 mg dose. (See '462 patent at col. 20 l. 61 – col. 23 l. 26, Table 1.)

This situation is on all fours with the recent Federal Circuit decision in *Biogen Int'l GMBH v. Mylan Pharms. Inc.* holding that “the district court did not clearly err in finding that a skilled artisan would not have recognized, based on the single passing reference to [the claimed] dose in the disclosure, that [the claimed dose] would have been efficacious in the treatment of MS, particularly because the specification's only reference to [the claimed dose] was part of a wide [dosage range and not listed as an independent therapeutically efficacious dose.” 18 F.4th 1333, 1343 (Fed. Cir. 2021). Claims 1, 3, 4, 5, and 7 of the '462 patent are thus invalid for lack of written description for the 1.0 mg limitation.

3. The claims of the '462 patent are invalid for lack of utility

For the same reasons as discussed above with respect to written description, the claims of the '462 patent are also invalid under 35 U.S.C. § 101 for lack of utility. *See, e.g., In re '318 Pat. Infringement Litig.*, 583 F.3d 1317, 1324-27 (Fed. Cir. 2009) (invalidating claims directed to methods of treating Alzheimer's disease and related dementias using galanthamine—including

claims directed to specific dosages of the compound—for failure to provide *in vitro* or *in vivo* test results demonstrating the utility of the compound). Thus, the Claims 1, 3, 4, 5, and 7 of the '462 patent are invalid for lack of utility.

4. The claims of the '462 patent are invalid for indefiniteness

The claims of the '462 patent are invalid as indefinite under 35 U.S.C. § 112. The claims recite methods of treating type 2 diabetes by administering 1.0 mg of semaglutide once weekly. However, the “treatment” of type 2 diabetes is ambiguous and does not allow a POSA to reasonably ascertain the boundaries of the claim because “treatment” could mean any one or more of the full spectrum of treatments, including the prevention of type 2 diabetes. (See '462 patent at col. 5 ll. 16-31 (describing a “full spectrum of treatments”).) Accordingly, a POSA would need to understand the full spectrum of treatments, and also how to treat a condition that has been prevented from occurring. Thus, the specification creates confusion, a POSA would not be reasonably certain about the scope of these claims and therefore, claims 1, 3, 4, 5, and 7 are indefinite for at least this reason.

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Based upon the information presently available to Defendants and based upon Defendants' initial understanding of the scope and construction of the asserted claims of the Asserted Patents, and of Plaintiffs' apparent positions concerning the scope and construction of the asserted claims

of the Asserted Patents, the asserted claims of the Asserted Patents are invalid at least on the grounds set forth above and in Exhibits A-G. Discovery and Defendants' investigation are ongoing, and Defendants reserve the right to modify and/or supplement its Invalidity Contentions as discovery progresses, after claim construction, or otherwise as appropriate.

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CERTIFICATE OF SERVICE

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