

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

Pursuant to Paragraph 6 of the Scheduling Order, 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 Nordisk A/S (collectively, "Novo") its invalidity contentions for the asserted claims of United States Patent Nos. 8,114,833

claim limitation is anticipated by, and therefore not patentably distinct from, an earlier species claim.”).

For at least these reasons, claims 1-3 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 are obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009, optionally in view of one or more of WO '530, the '833 Patent, WO '471, and Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

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

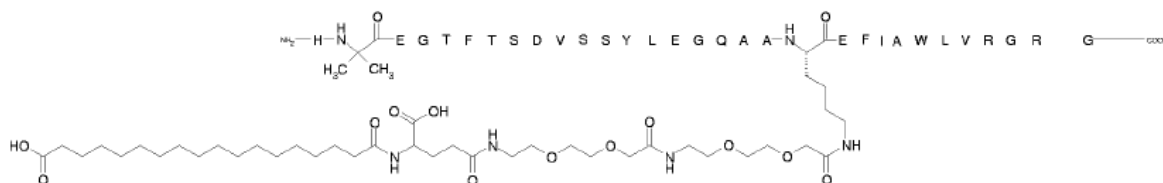
prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity” (WO ’537 at 37:34-36; US ’478 at [0191]; ’343 patent at col. 53 ll. 4-7.)

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]acetyl)amino]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.)

WO '530 describes pharmaceutical compositions for the treatment of type 2 diabetes comprising therapeutic peptides, such as semaglutide, that “may be administered orally, parenterally (e.g., via intravenous, subcutaneous, intracutaneous, intramuscular, intraarticular,

intraarterial, intrasynovial, intrasternal, intrathecal, intralesional, intraocular, or intracranial injection).” (WO ’530 at 88-89, 143; *see also id.* at 144 (“In some cases, in order to prolong the effect of a drug, it is desirable to slow the absorption of the agent from subcutaneous or intramuscular injection.”).)

WO ’471 discloses the use of a parenteral formulation of semaglutide for the treatment of type 2 diabetes. (*See* WO ’471 at 18:7-19, 24:30-31.)

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:

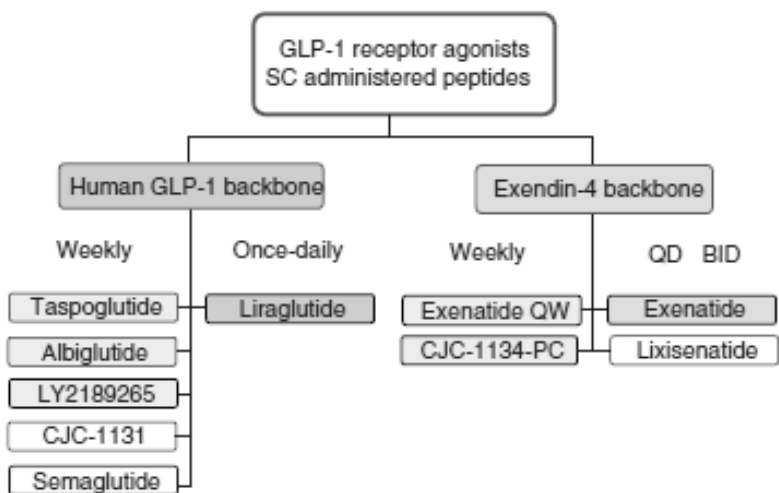


Figure 1. Shows the glucagon-like peptide-1 (GLP-1) receptor agonists, which have already been approved (exenatide BID and liraglutide). The agonists are subdivided in relation to whether the backbone of the compound is human GLP-1 or exenatide, and in relation to the frequency of administration (once 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 ’537,¹³ WO ’530, the ’833 Patent, WO ’471, 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, WO ’530, the ’833 Patent, WO ’471, 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.

Claims 1-3 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 1-3 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,

¹³ “WO ’537” refers to WO ’537 or US ’478 or the ’343 patent, here and below.

WO '530, the '833 Patent, WO '471, and Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

2. Claim 4 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, 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.)

WO '530 discloses the use of phosphate buffers and isotonicity agents, and expresses the goal of creating a pharmaceutical composition for parenteral administration that is “isotonic with the blood of the intended recipient.” (WO '530 at 53-54, 141, 143-44.)

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

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, WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

3. Claim 5 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, 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.)

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 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 one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

4. Claim 6 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, 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.)

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.

For at least these reasons, and the reasons discussed above with respect to claims 1-4, claim 6 patent 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 '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

5. Claim 7 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

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.)

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.)

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 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 and 6, 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 one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

6. Claim 8 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

Claim 8 depends from claim 4 and adds the limitation “wherein the phosphate buffer is a sodium dihydrogen phosphate buffer.” ('462 patent at col. 36 ll. 44-45.)

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 understand that a sodium dihydrogen phosphate buffer could be used in place of the disodium phosphate dihydrate buffer in the above solution.

The '833 patent also teaches the use of sodium dihydrogen phosphate buffer:

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 (emphasis added).)

Example 4 in the '833 patent also discloses a composition containing sodium dihydrogen phosphate. (*Id.* at col. 20 l. 31.)

WO '537 (or US '478 or the '343 patent) 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.)

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 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 use sodium dihydrogen phosphate buffer as the phosphate buffer in this formulation. 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.)

For at least these reasons, and the reasons discussed above with respect to claims 1-4, claim 8 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 '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

7. Claim 9 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art

Claim 9 depends from claim 1 and adds the limitation “wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at [sic] a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.” ('462 patent at col. 36 ll. 46-51.)

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 understand that a sodium dihydrogen phosphate buffer could be used in place of the disodium phosphate dihydrate buffer in the above solution.

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 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 (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.)

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.)

WO '530 discloses the use of phosphate buffers and isotonicity agents, and expresses the goal of creating a pharmaceutical composition for parenteral administration that is “isotonic with the blood of the intended recipient.” (WO '530 at 53-54, 141, 143-44.)

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

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.)

The ’833 patent also teaches the use of sodium dihydrogen phosphate buffer:

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 (emphasis added).)

Example 4 in the ’833 patent also discloses a composition containing sodium dihydrogen phosphate. (*Id.* at col. 20 l. 31.)

WO ’537, US ’478, and the ’343 patent disclose:

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.)

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 claims 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 in an isotonic aqueous solution comprising propylene glycol, phenol, and a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0 and would have reasonably expected such a formulation to prevent clogging of the injection device. 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.*, 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). The 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.)

For at least these reasons, and the reasons discussed above with respect to claims 1-3, claim 9 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 '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, in view of the knowledge of a person of ordinary skill in the art.

8. Claim 10 is obvious over WO '421, NCT00696657, WO '537 and/or Lovshin 2009 in combination with one or more of WO '530, the '833 Patent, and WO '471, optionally in view of Madsbad 2011, and the knowledge of a person of ordinary skill in the art

Claim 10 depends from claim 9 and adds the limitation “wherein the pH is 7.4.” ('462 patent at col. 36 ll. 52-53.)

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

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.

/s/ Kelly F. Farnan

Kelly E. Farnan (#4395)
Sara M. Metzler (#6509)
RICHARDS, LAYTON & FINGER, P.A.
One Rodney Square
920 North King Street
Wilmington, DE 19801
302-651-7705
farnan@rlf.com
metzler@rlf.com

*Attorneys for Defendants Sun Pharmaceutical
Industries Ltd. and Sun Pharmaceutical
Industries Inc.*

/s/ Pilar G. Kraman

Pilar G. Kraman (#5199)
YOUNG CONAWAY STARGATT
& TAYLOR, LLP
Rodney Square
1000 North King Street
Wilmington, DE 19801
(302) 571-6600
pkraman@ycst.com

*Attorneys for Defendants Zydus Worldwide
DMCC, Zydus Pharmaceuticals (USA) Inc.,
and Zydus Lifesciences Limited*

/s/ Dominick T. Gattuso

Dominick T. Gattuso (#3630)
HEYMAN ENERIO GATTUSO
& HIRZEL LLP
300 Delaware Avenue, Suite 200
Wilmington, DE 19801
(302) 472-7300
dgattuso@hegh.law

*Attorneys for Defendants Dr. Reddy's
Laboratories, Ltd. and Dr. Reddy's
Laboratories, Inc.*

/s/ Stamatios Stamoulis

Stamatios Stamoulis (#4606)
Richard C. Weinblatt (#5080)
STAMOULIS & WEINBLATT LLC
800 N. West Street, Third Floor
Wilmington, DE 19801
(302) 999-1540
stamoulis@swdelaw.com
weinblatt@swdelaw.com

*Attorney for Defendant
Mylan Pharmaceuticals, Inc.*

/s/ Nathan R. Hoeschen

Karen E. Keller (No. 4489)
Nathan R. Hoeschen (No. 6232)
Emily S. DiBenedetto (No. 6779)
SHAW KELLER LLP
I.M. Pei Building
1105 North Market Street, 12th Floor
Wilmington, DE 19801
(302) 298-0700 kkeller@shawkeller.com
nhoeschen@shawkeller.com
edibenedetto@shawkeller.com

Attorneys for Defendant Alvogen

/s/ Kenneth L. Dorsney

Kenneth L. Dorsney (#3726)
Cortlan S. Hitch (#6720)
MORRIS JAMES LLP
500 Delaware Avenue, Suite 1500
Wilmington, DE 19801
(302) 888-6800
kdorsney@morrisjames.com
chitch@morrisjames.com

*Attorneys for Defendants Rio
Pharmaceuticals, Inc. and EMS S/A*

CERTIFICATE OF SERVICE

I hereby certify that on October 20, 2022, true and correct copies of the foregoing document were caused to be served on the following counsel of record as indicated:

BY ELECTRONIC MAIL

Jack B. Blumenfeld
Jeremy A. Tigan
Travis J. Murray
Morris, Nichols, Arsht & Tunnell LLP
1201 North Market Street
Wilmington, DE 19801

BY ELECTRONIC MAIL

Jeffrey J. Oelke
Ryan P. Johnson
Robert E. Counihan
Laura T. Moran
Erica R. Sutter
Olivia L. Wheeling
Fenwick & West LLP
902 Broadway, Suite 14
New York, NY 10010-6035

/s/ Kelly E. Farnan

Kelly E. Farnan (#4395)
farnan@rlf.com