UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00724

Patent No. 10,335,462

DECLARATION OF PAUL DALBY, PH.D., IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 10,335,462

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TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation
U.S. Patent No. 5,164,366	’366 patent
U.S. Patent Application Pub. No. US2007/0010424	’424 publication
U.S. Patent No. 10,335,462	’462 patent
U.S. Patent No. 5,512,549	’549 patent
U.S. Patent No. 5,118,666	’666 patent
U.S. Patent No. 7,022,674	’674 patent
U.S. Patent No. 6,284,727	’727 patent
U.S. Patent No. 6,458,924	’924 patent
U.S. Patent No. 6,268,343	Knudsen patent
Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)	Lovshin
Lund, *Emerging GLP-1Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)	Lund
Boylan, *Parenteral Products*, *in* MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)	Modern Pharmaceutics
Clinical Trial No. NCT00696657	NCT657
Clinical Trial No. NCT00851773	NCT773
Ozempic prescribing information (Oct. 2022)	Ozempic label
REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)	Remington
Victoza, PHYSICIANS’ DESK REFERENCE (65th ed. 2010)	Victoza label
WO 00/37098	WO098
WO 03/002136	WO136
WO 2011/058193	WO193
WO 2011/073328	WO328
WO 2011/138421	WO421
WO 2006/097537	WO537

1. My name is Paul Dalby, Ph.D. I have been retained by Mylan Pharmaceuticals Inc. ("Mylan") to provide my expert opinions regarding the unpatentability of U.S. Patent No. 10,335,462 ("'462 patent") (Ex. 1001). I understand that Mylan intends to petition for *inter partes* review ("IPR") of the '462 patent, which is assigned to Novo Nordisk A/S. I also understand that, in the IPR petition, Mylan will request that the United States Patent and Trademark Office cancel all claims of the '462 patent as unpatentable. I submit this expert declaration to address and support Mylan's IPR petition for the '462 patent.

I. QUALIFICATIONS AND BACKGROUND

A. Education and Experience; Prior Testimony

2. I earned my doctorate at Cambridge University, UK, in 1998 where I studied protein folding mechanisms, using protein engineering to alter the relative stabilities of the native, denatured, intermediate and transition states, and evaluating the effects of a range of temperature, pH and presence of viscosity modifiers in the formulation. From 1998 to 2000, I was a postdoctoral fellow at the University of Pennsylvania, where I studied the relationship between protein structure, stability and function through protein engineering and biophysical characterisation, and also methods to improve stability and minimize aggregation in protein therapeutic formulations. In 2000, I was appointed Lecturer at University College London (UCL) in the Department of Biochemical Engineering. My research focused on new

strategies for evolutionary protein and enzyme design, researching factors to strengthen protein stability during biopharmaceutical downstream processes, and developing stability analysis methods to optimise the process and maintain proper protein formulation.

3. From 2004-2006, I was principal investigator on a project funded by the Department of Trade and Industry in conjunction with the Health Protection Agency, UK, to establish protein, process, and formulation engineering methods for novel protein fusions. During that time, I was an active member of the Protein Society, the Royal Society of Chemistry, the RSC Biotechnology Group Committee, the Institution of Chemical Engineers, and the American Chemical Society. I organized conferences on behalf of these organizations including the 2006 "Therapeutic Proteins: Chemical & Enzymatic Modification" in London. Based on my work with the previous organizations, I was invited to a joint BIA & Bioprocess UK workshop in 2005. The workshop led to the establishment of biopharmaceutical formulation as a funding priority in the DTI technology transfer program.

4. In 2006, I began a long-term collaboration with the National Institute of Biological Standards and Controls in the UK to improve the tools and techniques used in liquid and freeze-dried protein formulation development. The projects undertaken used biophysical analysis and statistical design of experiments

approaches, to optimise formulations, and to characterise and understand the impact of different excipients on their properties.

5. In 2007, I was appointed Senior Lecturer at UCL and in 2009 I was appointed Reader at UCL in the Department of Biochemical Engineering. From 2011 until 2016, I was Co-Director of the Engineering and Physical Sciences Research Council (EPSRC) Centre for Innovative Manufacturing at UCL.

6. I am currently Co-Director of the EPSRC Future Targeted Healthcare Manufacturing Hub and Director of the EPSRC Doctoral Training Centre for Innovative Manufacturing at UCL. In 2013, I was appointed Professor at UCL, Department of Biochemical Engineering, and in 2016 was named Deputy Head, Department of Biochemical Engineering (Research) at UCL. Over the course of my career at UCL, I have supervised numerous projects resulting in novel research and development in the field of protein stability. These projects resulted in developing a novel method for measuring protein stability in microtiter plates; development of enhanced bioprocessing for advanced pharmaceutical proteins, using directed evolution; and new methods of protein engineering and formulation resulting in improved biopharmaceutical stability. The various projects are listed in my CV. I have presented the results of my research on protein therapeutics and formulation at numerous international conferences including the Protein Science Forum 2005, the Cambridge Healthtech Institute 2006, ACHEMA 2006, BioProcess International

2007, 2011 & 2012, Recovery XIV 2010, World Biopharm Forum 2011, and the Royal Society of Chemistry MiBIO 2012.

7. I am considered a key influencer of research priorities in the UK in the area of biopharmaceutical formulation. I have been appointed to lead government and industry groups for establishment of biopharmaceutical formulation protocols. I have provided consultancy services to a number of companies, including: Ajinomoto, Angel Biotechnology, Cambridge Antibody Technology (now MedImmune and owned by AstraZeneca), and Clear Capital Ltd. I also serve on the Scientific Advisory Board for Leukocare GmbH in Germany, and UMabs in the USA and China, and have presented my work at international conferences on biopharmaceutical formulation development.

8. I have been given numerous research grants to research and supervise projects impacting the biochemical protein industry. My research interests include: accelerating therapeutic protein and vaccine formulation design for stability in both liquid and lyophilized forms; biophysical characterisation of protein aggregation and stability in formulations and bioprocess manufacturing; protein engineering for stability; using directed evolution, structural analysis, bioinformatics and computational design, high-throughput bioprocess design, including precipitation and inclusion body refolding; design and development of novel analytical methods for bioprocess monitoring and characterisation of formulations.

9. In the previous four years, I have provided testimony in the following proceedings:

- *Celltrion, Inc. v. Genentech, Inc. et al.*, IPR2022-00578 (PTAB);
- *XOMA (US) LLC v. MorphoSys AG*, Case No. 01-21-0004-4508 (ICDR, Nov. 2022);
- *Novo Nordisk Inc. v. Mylan Institutional LLC*, C.A. No. 1:19-cv-01551-KAJ-SRF (D. Del.); and
- *Merck & Co Inc. v. Wyeth*, NSD1381/2017 (Australia).

10. My qualifications are further described on my *curriculum vitae*, found at Exhibit 1008.

B. Basis for Opinions and Materials Considered

11. Exhibit A includes a list of the materials I considered, in addition to my experience, education, and training, to provide the opinions contained in this declaration.

C. Retention and Compensation

12. Mylan retained me as a technical expert to provide various opinions about the '462 patent. I am being compensated at a rate of 360 GBP per hour plus expenses for this work. My compensation is in no way tied to the outcome of this proceeding or to the content of this declaration, and it has not altered my opinions.

II. SUMMARY OF OPINIONS

13. My opinions are limited to semaglutide formulations used in the treatment of diabetes, as claimed in the ’462 patent. I present my opinions from the perspective of a POSA, who is defined in Section IV.

14. I understand that Mylan’s expert Dr. John Bantle offers the opinions that it would have been obvious to a POSA to treat diabetes with a once-weekly, 1.0 mg semaglutide injectable formulation, as recited in the limitations of claims 1–3, containing the components recited in claims 4–10 (which I address herein), with a reasonable expectation of success in doing so.

15. Based on my view of the prior art and, for certain claims, Dr. Bantle’s additional views of the prior art, it is my opinion that the claims of the ’462 patent would have been obvious over the following combinations of references:

a) Claims 4–10 of the ’462 patent would have been obvious over WO421 considering the ’424 publication (Ground 3) or over NCT657 and NCT773 considering the ’424 publication (Ground 5); and

b) Claims 4–10 of the ’462 patent would have been obvious over WO537 considering Lovshin (Ground 4).

16. These references would have motivated a POSA to formulate a 1.0 mg semaglutide injectable formulation containing the components recited in claims 4–

10 to treat type 2 diabetes, as described by Dr. Bantle (claims 1–10), with a reasonable expectation of success doing so.

17. I understand that Patent Owner may present expert opinions regarding "secondary considerations" of non-obviousness of the formulations recited in the method of treatment claims in response to my declaration, and that I may be asked to address such opinions in the future. I therefore expressly reserve the right to address later all issues of secondary considerations that Patent Owner's experts may raise.

III. LEGAL STANDARDS

18. To prepare and form my opinions set forth in this declaration, I have been informed of the relevant legal principles.[1] I applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below.

[1] To support my analysis and to help me reach my opinions and conclusions, I was informed of and advised to apply various legal principles relating to unpatentability, which I set forth here. By setting forth these legal standards, I do not intend to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I provide in this case.

19. I have been informed that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. I have been told that this means it must be more likely than not that the claims are unpatentable.

20. I understand that my opinions regarding unpatentability are from the viewpoint of a person of ordinary skill in the art ("POSA") in the field of technology of the patent as of the patent's priority date. I have also been informed by counsel that when defining a POSA, the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field. Further, I understand a POSA is generally skilled in the relevant art (i.e., the subject matter claimed and described in the patent).

21. I am told that for a patent to be anticipated, a prior art reference must disclose all elements of that claim expressly and/or inherently as arranged in the claim. With respect to inherent disclosure, there is no requirement that a POSA would have recognized the inherent disclosure at the time of the invention, but only that the subject matter is in fact inherent, or necessarily present, in the prior art reference.

22. I am told that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the

claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

23. I understand that when there is some recognized reason to solve a problem, and there are a finite number of identified, predictable, and known solutions, a person of ordinary skill in the art has good reason to pursue the known options within his or her technical grasp. If such an approach leads to the expected success, it is likely not the product of innovation but of ordinary skill and common sense. I understand that any need or problem known in the field of endeavor at the time of invention or addressed by the patent can provide a reason for combining prior art elements to arrive at the claimed subject matter. I understand that only a reasonable expectation of success is necessary to show obviousness.

IV. PERSON OF ORDINARY SKILL IN THE ART

24. In my opinion, the following definition of a person of ordinary skill in the art applies to the claims of the '462 patent. I reserve the right to amend and/or supplement my opinions on unpatentability if a different definition of a POSA is adopted or agreed to.

25. A POSA would have understood the prior art references referred to herein and would have the capability to draw inferences from the prior art references. It is understood that, to the extent necessary, a POSA may collaborate with one or more other POSAs for one or more aspects with which the other POSA may have

expertise, experience, and/or knowledge. Additionally, a POSA could have had a lower level of formal education than what I describe in the following definition if the person has a higher degree of experience. In view of the relatively high level of skill and the clear teachings in the prior art, the level of skill of a POSA is not dispositive of any issue raised in this Petition.

26. In my opinion, the following definition of a POSA applies to the claims of the '462 patent. A POSA would have (1) an M.D., Pharm.D., or Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

27. Alternatively, a POSA would be (1) a highly-skilled scientist lacking an M.D., Pharm.D., or Ph.D., but would have (2) more than five years of experience in the area of protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and/or (3) experience with the development, design, manufacture, or formulation of therapeutic agents, and the literature concerning protein or peptide formulation and design or diabetes treatments. In either case, a

higher educational level could substitute for some amount of the requisite experience.

28. As explained above, and as is evident from my CV, I met the qualifications of a POSA as of the priority date of the ’462 patent.

V. THE ’462 PATENT (EX. 1001)

29. I have read the ’462 patent, which is titled “Use of Long-Acting GLP-1 Peptides,” including its claims, and reviewed relevant portions of the file history of the ’462 patent (Ex. 1002).

30. I have assumed that the earliest priority date to which the asserted claims of the ’462 patent are entitled is July 1, 2012, which is the date recited on the face of the patent for foreign reference EP12174535, listed under “Foreign Application Priority Data.” To the extent Patent Owner later asserts and/or proves that the asserted claims are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

A. The Formulation Claims of the ’462 Patent

31. The ’462 patent has one independent claim, which recites:

> 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.

32. Dependent claims 4–10 depend from claim 1, directly or indirectly, and are provided below.

33. Dependent claim 4 recites:

> 4. The method according to claim 1, 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.

34. Dependent claim 5 recites:

> 5. The method according to claim 4, wherein the solution further comprises propylene glycol and phenol.

35. Dependent claim 6 recites:

> 6. The method according to claim 4, wherein the pH is 7.4.

36. Dependent claim 7 recites:

> 7. The method according to claim 6, wherein the solution further comprises propylene glycol and phenol.

37. Dependent claim 8 recites:

> 8. The method according to claim 4, wherein the phosphate buffer is a sodium dihydrogen phosphate buffer.

38. Dependent claim 9 recites:

9. The method according to claim 1, wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol.

39. Dependent claim 10 recites:

10. The method according to claim 9, wherein the pH is 7.4.

B. The Prosecution History of the '462 Patent

40. When the application for the '462 patent was filed on July 21, 2017, independent claim 1 recited:

1. A method for

a) reduction of HbA1c;

b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or

c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;

wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof, wherein said GLP-1 agonist

i) has a half-life of at least 72 hours;

> ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0. 7 mg semaglutide per week; and
>
> iii) is administered once weekly or less often.

Ex. 1002 at 8.

41. The Examiner rejected the filed claims on July 23, 2018, based on NCT00696657, which disclosed the use of semaglutide and liraglutide, Madsbad (2011), which disclosed the use of several GLP-1 agonists, and Kim (2007), which disclosed the use of exenatide, anticipated the claims because they each disclosed a method of treatment with at least 0.8 mg of GLP-1 agonist once weekly (NCT657 with 0.8 mg semaglutide; Madsbad with 4, 15, and 30 mg albiglutide; and Kim with 0.8 and 2.0 mg exenatide), with all the other requirements satisfied (treating type 2 diabetes and reducing HbA1c, with a half-life in the required range, etc.). *See* Ex. 1002 (July 23, 2018 Office Action) at 312.

42. The applicants then amended claim 1 to recite:

> 1. (Currently Amended) A method for <u>treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof</u>
>
> ~~a) reduction of HbA1c;~~
>
> ~~b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or~~

> ~~c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;~~
>
> ~~wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,~~
>
> ~~wherein said GLP-1 agonist~~
>
> ~~i) has a half-life of at least 72 hours;~~
>
> ~~ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and~~
>
> ~~iii) is administered once weekly or less often~~.

See Ex. 1002 (January 23, 2019 listing of claims) at 332.

43. The applicants also filed a terminal disclaimer over U.S. Patent No. 9,764,003, which claims "[a] method for reducing body weight, comprising administering [only] semaglutide once weekly in an amount of at least 0.7 mg and up to 1.6 mg to a subject in need thereof." *See* Ex. 1002 (February 28, 2019 Terminal disclaimer) at 336.

44. The Examiner then withdrew the anticipation rejections and allowed the claims, stating:

> The '657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The semaglutide or liraglutide was used as on add-on therapy

> to type 2 diabetic patients already taking metformin. Efficacy of treatment was further assessed by a reduction in HbA1c levels. Patients in the Arm Labels D and E of the clinical trial were administered 0.8 mg once weekly by subcutaneous injection. However, the reference does not teach or disclose a higher amount of 1 mg semaglutide.

See Ex. 1002 (March 6, 2019 Notice of Allowance) at 344-45.

VI. CLAIM CONSTRUCTION

45. I have been informed that claim terms should be given their plain and ordinary meaning in light of the intrinsic evidence (i.e., the specification and the prosecution history) from the perspective of a POSA. I also understand that while extrinsic evidence (e.g., scientific publications) may be considered when interpreting the meaning of claim terms in some circumstances, it is generally given less weight than intrinsic evidence. I am not offering any opinions related to claim construction because in my view all the claim terms related to pharmaceutical formulations can be understood based on their plain and ordinary meaning. I understand that others are offering opinions related to methods of treatment.

VII. BACKGROUND ON GLP-1 COMPOUND FORMULATIONS USED TO TREAT DIABETES

A. Parenteral formulations and components thereof were well-known

46. Substantial guidance was available to POSAs to prepare parenteral formulations well before the priority date of the '462 patent. For example, POSAs were well-aware that parenteral formulations can be administered though intravenous, subcutaneous, intradermal, intramuscular, intraarticular, and intrathecal injection. Ex. 1069 (Remington) at 37; Ex. 1070 (Modern Pharmaceutics) at 8-9 (Table 1). POSAs were well aware of the various components that were important for preparing successful parenteral formulations. For example, POSAs understood that "[s]olutions to be administered subcutaneously require strict attention to tonicity adjustment, otherwise irritation of the plentiful supply of nerve endings in this anatomical area would give rise to pronounced pain." Ex. 1069 (Remington) at 37; *see also* Ex. 1070 (Modern Pharmaceutics) at 22. Thus, POSAs were aware of the importance of using isotonic agents, such as sodium chloride, in parenteral formulations to prevent osmotic pressure changes upon injection. Ex. 1070 (Modern Pharmaceutics) at 18-19 (Table 2), 22. POSAs were also aware of the importance of including a preservative, such as phenol or cresol, in the parenteral preparation to prevent the growth of microorganisms. Ex. 1069 (Remington) at 41; Ex. 1070 (Modern Pharmaceutics) at 18-19 (Table 2). Finally, the importance of buffers to

maintain product stability in parenteral formulations was also well-known to POSAs. Ex. 1069 (Remington) at 41-42; Ex. 1070 (Modern Pharmaceutics) at 20.

47. The prior art also taught 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. *See, e.g.*, Ex. 1071 ('727 patent) at 1:38-54, 17:8-10. GLP-1 derivative solutions included the various well-known components for parenteral formulations such as buffers, preservatives, isotonic agents, and vehicles. *See, e.g.*, *id.* at 17:32-36, 18:44-61. Similar parenteral solutions were well-known in the art and were used with other peptide solutions, such as insulin solutions. Ex. 1072 ('366 patent) at 7:64-8:10, 17:15-22.

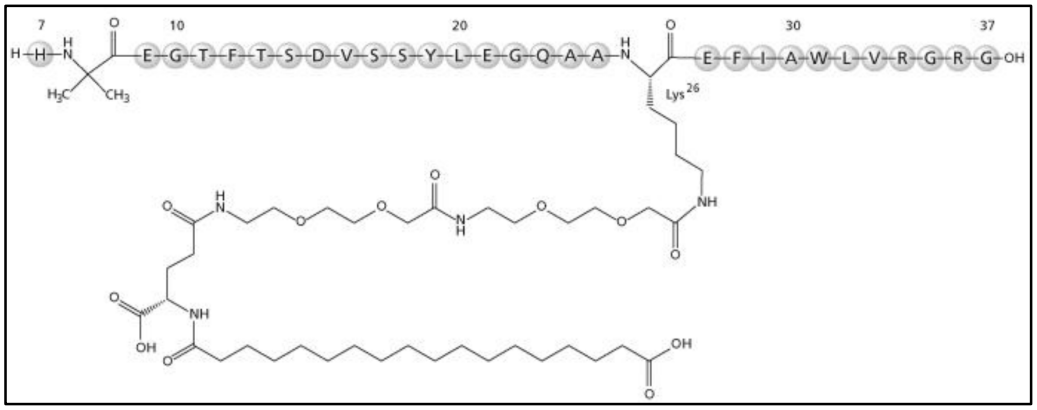
B. GLP-1 compounds were well-known

48. Before the priority date of the '462 patent, POSAs were aware of the two different forms of naturally occurring glucagon-like peptide-1 (GLP-1): GLP-1(7-36) and GLP-1(1-37). Ex. 1034 (Knudsen patent) at 4:48-60.

49. POSAs were also aware of an FDA-approved GLP-1 receptor agonist for controlling type-2 diabetes and weight loss—Victoza®, which was approved by FDA in 2010. Ex. 1039 (Victoza label) at 2, 5 ("Victoza contains liraglutide, an analog of human GLP-1" that "acts as a GLP-1 receptor agonist.").

50. Liraglutide was available as a solution for subcutaneous injection in a pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg. *Id.* at 2. Victoza® contains the following inactive ingredients: disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection. *Id.* at 5.

51. The semaglutide peptide is very similar to the liraglutide peptide. Semaglutide has the following structure:



Ex. 1081 (Ozempic label) at 12.[2] The differences between semaglutide and liraglutide include: (1) semaglutide has an aminoisobutyric acid at position 8 rather

[2] I have used an image from the Ozempic label as a convenient graphic to show the structure of semaglutide. The Ozempic label however is not prior art here, and I do not rely on the Ozempic label for my obviousness opinions. The structure of semaglutide was in the prior art, and known to be as shown on the later-published

than the alanine in liraglutide, (2) semaglutide has a di-AEEA spacer that connects a glutamic acid linker and a fatty acid to Lys^{26}, and (3) there is a C_{18} dicarboxylic acid rather than a C_{16} monocarboxylic acid at Lys^{26} (i.e., semaglutide adds one carboxylate group to the terminal end of the fatty acid). Compare *id.* with Ex. 1032 (Knudsen 2004) at 3 or Ex. 1033 (Knudsen 2010) at 31 (both showing liraglutide's alanine-containing amino acid sequence with a C16 fatty acid side chain and glutamic acid linker).

52. As discussed above, before the priority date of the '462 patent, POSAs were provided with substantial guidance to prepare parenteral formulations. *See, e.g.,* Ex. 1069 (Remington); Ex. 1070 (Modern Pharmaceutics).

53. In addition, before the priority date of the '462 patent, formulations containing GLP-1-related compounds, including semaglutide, were well-known in the art. For example, prior art references disclosed injectable GLP-1 compound formulations and inactive ingredients such as a buffer, an isotonicity agent, and preservatives. *See, e.g.*, Ex. 1041 (WO136) at 2:4-5, 19:26-34, 20:34-21:4; Ex. 1034 (Knudsen patent) at 217:24-55, 219:26-45, 220:61-221:18; Ex. 1073 ('924 patent)

Ozempic label. *See* Ex. 1057 (WO328) at 2:16-17 (identifying semaglutide in Example 4 of WO537); Ex. 1015 (WO537) at 48:4-22 (Example 4 with semaglutide structure); Ex. 1081 (Ozempic label).

at 153:45-56. The prior art also specifically taught that GLP-1 compounds could be formulated into these injectable formulations. Ex. 1034 (Knudsen patent) at 216:15-57; Ex. 1073 ('924 patent) at 153:45-56.

54. It was also well-known that GLP-1 compounds had problems with solubility and stability. *See, e.g.,* Ex. 1074 (WO098) at 3-4. Therefore, POSAs sought to optimise GLP-1 compound formulations to provide improved soluble and stable formulations. *See, e.g.*, Ex. 1034 (Knudsen patent) at 5:13-15; Ex. 1074 (WO098) at 7 ("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."); Ex. 1075 ('674 patent) 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.").

C. GLP-1 agonists and related formulations were well-known

55. As discussed above, before the priority date of the '462 patent, GLP-1 agonists and related formulations were well known in the art. Indeed, the '462 patent identifies "examples of suitable GLP-1 agonists." Ex. 1001 ('462 patent) at 8:53-55 (citing WO 2005/027978). The '424 publication also provided a list of prior art publications that include "suitable GLP-1 analogues and derivatives." *See* Ex. 1016 ('424 publication) at [0042] (citing WO93/19175, WO99/43705, WO 99/43706,

WO99/43707, WO98/08871, WO02/46227, WO99/43708, WO99/43341, WO87/06941, WO90/11296, WO91/11457, WO98/43658, EP0708179, EP0699686, and WO01/98331). The compound NN9535, otherwise known as semaglutide, was also known in the art. *See, e.g.*, Ex. 1035 (Lund) at 4; Ex. 1012 (Lovshin) at 2; Ex. 1015 (WO537).

D. Parenteral dosage forms for peptide-based drugs

56. Parenteral dosage forms are administered by injection, such as subcutaneous, intramuscular, intravenous, and intraarticular injections. Ex. 1069 (Remington) at 37. POSAs understood that parenteral dosage forms had several advantages in treating patients over non-parenteral formulations, which are administered generally via routes that require the drug compound to pass through protective mucosal membranes (e.g., orally, topically, vaginally, via the rectum). *Id.* at 36. For example, unlike oral drugs, parenteral dosage forms avoid passing through the digestive tract before being absorbed into the blood, which provides rapid distribution throughout the body that can result in earlier onset of therapeutic effects. Ex. 1070 (Modern Pharmaceutics) at 7-10. POSAs recognized that this was particularly beneficial for peptide-based drugs because it allowed the peptides to avoid degradation by gastric acid and potential elimination of therapeutic activity. Ex. 1069 (Remington) at 21, 27. 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. *Id.* at 37.

57. POSAs also recognized the benefits of subcutaneous injections over other parenteral dosage forms, such as intravenous injections. For example, 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. *Id*. Moreover, in contrast to intravenous injections, which require training for administration, subcutaneous injections are convenient, allowing for patient self-administration. *Id*.

58. POSAs would also be aware that careful consideration must be given to specific parameters, such as pH and tonicity, when developing the parenteral formulation to minimize potential adverse effects of tissue damage and injection pain. Ex. 1070 (Modern Pharmaceutics) at 43-45. Moreover, POSAs were aware of the need to prepare parenteral formulations under highly controlled and aseptic conditions to avoid potential microbial infection when injected. Ex. 1069 (Remington) at 37, 41. Because parenteral dosages are often intended for multiple dosing, POSAs would have been aware that anti-microbial excipients may be necessary in the formulation. *Id.* at 41. POSAs would also recognize the importance of maintaining the physical and chemical stability of the drug formulation to

minimize the risk of impurities during manufacturing, storage, and handling. Ex. 1069 (Remington) at 41; Ex. 1070 (Modern Pharmaceutics) at 7-10.

59. 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. Ex. 1069 (Remington) at 16-27; Ex. 1070 (Modern Pharmaceutics) at 43-45.

1. Tonicity and osmolarity of the parenteral formulation

60. Tonicity of a formulation relates to its osmotic pressure, osmolarity and osmolality, as compared to that of a physiological fluid. Ex. 1070 (Modern Pharmaceutics) at 43-44. POSAs would have been aware that a parenteral formulation should be "isotonic" with body fluids to minimize the risk of injury, because hypertonic and hypotonic formulations can cause undesirable complications such as tissue damage and hemolysis, in addition to pain or irritation at the site of administration. Ex. 1069 (Remington) at 41; Ex. 1070 (Modern Pharmaceutics) at 22, 43-44. POSAs preparing parenteral formulations would have been very familiar with calculating the concentration of an isotonicity agent needed to achieve a specific osmolarity by using texts such as Modern Pharmaceutics to prepare formulations that are isosmotic and/or isotonic with physiological fluids. Ex. 1070 (Modern Pharmaceutics) at 43-44.

2. pH and buffering capacity of the parenteral formulation

61. POSAs would also have been aware of the importance of buffers to maintain the pH of a 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 (Ex. 1057 (WO328) at 12:31), 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. Ex. 1070 (Modern Pharmaceutics) at 22, 39; Ex. 1069 (Remington) at 20.

62. POSAs were also aware of using phosphate as the buffer, such as sodium dihydrogen phosphate. WO136 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." Ex. 1041 (WO136) at 18:27-30. WO136 further described "glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, [and] sodium phosphate" as "preferred." *Id*. at 18:30-33.

63. POSAs would be aware that extreme values of pH, such as 2.3 and 11, may result in tissue injury and cell death. Ex. 1070 (Modern Pharmaceutics) at 43-45. 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* Ex. 1069 (Remington) at 20; Ex. 1070 (Modern Pharmaceutics) at 43-45.

3. Avoiding particulates in the parenteral formulation

64. POSAs were aware of the disadvantages of the introduction of particulates, including insoluble matter, in formulations or formulation containers, or excipient or drug components that have come out of solution due to, for example, degradation, aggregation, chemical reactions, interactions with the container, temperature extremes, or limited solubility, in parenteral dosage forms. Unintended particulates in a parenteral formulation could lead to loss of drug activity, irritation at the patient's injection site, immunological sensitisation to the drug compound and/or the excipients, anaphylactic shock, and/or cause an embolism or vessel blockage if the particulate enters the blood. *See* Ex. 1069 (Remington) at 60-61. Thus, POSAs sought to minimise particulate formation during preparation and manufacture of the formulation. Ex. 1069 (Remington) at 60-61; Ex. 1070 (Modern Pharmaceutics) at 24-26.

4. Vehicles and diluents of the parenteral formulation

65. POSAs were aware that vehicles provide a liquid carrier for the drug in parenteral formulations and are necessary for most parenteral delivery routes. Ex. 1069 (Remington) at 39-41. 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*. A POSA would have known that 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.*; Ex. 1070 (Modern Pharmaceutics) at 23. Nevertheless, some drug molecules may be non-polar and have insufficient solubility in water, in which case an organic co-solvent may be used with the water to lower the vehicle polarity and increase drug solubility. Related, a POSA would have known that where water alone is insufficient for the formulation of a parenteral drug, the POSA could calculate (for example, from the partition coefficient, LogP), whether a drug is non-polar and modify the vehicle accordingly. Ex. 1069 (Remington) at 39-41.

66. POSAs would have been aware of the use of organic solvents to improve solubility in FDA-approved formulations. Moreover, guidance on the use of non-aqueous solvents in parenteral formulations would have been readily available using texts such as Martin's Physical Pharmacy and Remington's Pharmaceutical Sciences. Ex. 1069 (Remington) at 41.

5. Excipients of the parenteral formulation

67. POSAs also carefully considered how 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 when designing peptide formulations. For example, addition of an excipient known to provide a stabilizing effect to a peptide drug, such as propylene glycol, could stabilize a peptide drug formulation.

68. Because excipients can have profound effects on the performance of a drug, POSAs understood that it was important that parenteral preparations are "of the very best quality and provide the maximum safety for the patient." Ex. 1069 (Remington) at 37. 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. Ex. 1070 (Modern Pharmaceutics) at 18; Ex. 1069 (Remington) at 37-38.

69. Thus, POSAs 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. Consequently, POSAs knew that it would be preferable to minimize the number of excipients used in a parenteral dosage form. Ex. 1070 (Modern Pharmaceutics) at 18.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

70. I identify below the prior art references supporting my expert opinions on unpatentability of claims 4–10 of the '462 patent, including references rendering

the claim obvious. All the references I cite in this document would have been known, and publicly available, to a POSA as of the relevant priority date.

71. The prior art disclosures identified in this expert declaration would have been understood by a POSA in light of the background knowledge that he or she would have had by the applicable priority dates of the '462 patent. Thus, to the extent I list or describe a reference below but do not rely on it as a ground for arguing unpatentability, that prior art should be understood to form part of the background knowledge of a POSA, and to support that person's motivation to combine the prior art with a reasonable expectation of success. Further, to the extent I cite a reference for just one or several of its teachings, I reserve the right to rely on that reference for any other aspect of its teaching.

72. For every item of prior art, I reserve the right, as necessary, to establish that the subject matter I describe has an earlier effective date or date of first publication than indicated here. In addition to the references specifically recited herein, I rely generally on the knowledge of a POSA at the time of invention, including, without limitation, the knowledge described generally in this declaration (i.e., without referring to a specific document).

A. WO 2011/138421 ("WO421") (Ex. 1011)

73. International Patent Publication Number WO 2011/138421 ("WO421"), "Combination Therapy," published on November 10, 2011. WO421

identifies Boehringer Ingelheim International GMBH as the applicant and the inventors as Thomas Klein, Rolf Grempler, and Michael Mark.

74. WO421 disclosed "methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus" 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, to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof." Ex. 1011 (WO421) at 2:4-9.

75. WO421 further disclosed "[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide." *Id.* at 34:20-22. WO421 further disclosed that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13.

76. WO421 also 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." *Id.* at 40:23-26.

B. U.S. Patent Application Pub. No. US2007/0010424 ('424 publication) (Ex. 1016)

77. U.S. Patent Application Publication Number No. US2007/0010424 A1, entitled "Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices," published on January 11, 2007. Ex. 1016 ('424 publication) at 1. The '424 publication identifies Novo Nordisk, Inc. for the correspondence address and the inventors as Tina Bjeldskov Pedersen, Claude Bonde, and Dorthe Kot Engelund. *Id.*

78. The '424 publication disclosed "pharmaceutical formulations comprising a peptide and propylene glycol, to methods of preparing such formulations, and to uses of such formulations in the treatment of diseases and conditions for which use of the peptide contained in such formulations is indicated." *Id.* at Abstract.

79. The '424 publication explained that "[t]he formulations of the present invention may be formulated with any peptide where examples of such peptides include, but are not limited to … glucagon-like peptide-1 [i.e., GLP-1], glucagon-like peptide-2 … and analogues as well as derivatives thereof where each of these peptides constitutes an alternative embodiment of the present invention." *Id.* at [0038].

80. Regarding concentrations of the disclosed formulations, the '424 publication made clear that broad ranges could be acceptably formulated, including anywhere from "0.1 mg/ml to about 100 mg/ml, more preferably in a concentration from about 0.1 mg/ml to about 50 mg/ml, and most preferably in a concentration of from about 0.1 mg/ml to about 10 mg/ml." *Id.* at [0080].

81. Regarding various potential components of the formulation, the '424 publication disclosed that the formulation could contain propylene glycol in various concentrations, *id.* at [0103]–[0107], have a pH from 7.0 to 9.5, *id.* at [0108]–[0112], buffer, *id.* at [0114], and preservative ("well-known to the skilled person"), like phenol, *id.* at [0115]–[0117]. The '424 publication noted that "in a preferred embodiment, the formulations of the invention-contain, in addition to a peptide and propylene glycol, a buffer and/or a preservative." *Id.* at [0128].

82. As to uses of such formulations, the '424 publication disclosed that they "are optimal for production and for use in injection devices," for use in mammals, preferably humans, and, in a preferred embodiment, by subcutaneous injection, a form of parenteral administration. *Id.* at [0143]–[0145].

83. Example 3 in the '424 publication disclosed a formulation containing a GLP-1-related peptide, disodium hydrogen phosphate buffer, phenol, and mannitol or propylene glycol, at pH 8.15, with a suggestion to set the pH at 7.40, 7.70, or 7.90. *Id.* at [0205]–[0214].

84. Example 4 in the '424 publication disclosed a formulation containing liraglutide, disodium hydrogen phosphate buffer, sodium dihydrogen phosphate buffer, mannitol, and phenol, at pH 7.4. *Id.* at [0220]–[0227].

85. The claims published in the '424 publication included a pharmaceutical formulation with a GLP-1 agonist, propylene glycol (at a concentration from about 1 mg/ml to about 100 mg/ml), and a pH from about 7.0 to about 10.0. *Id.* at claim 12.

C. Clinical Trial No. NCT00696657 (NCT657) (Ex. 1013)

86. *A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide*, NCT00696657 ("NCT657"), is a clinical trial whose description was made available and listed on clinicaltrials.gov.[3] According to the face of NCT657, certain of its details were first submitted on June 11, 2008. Ex. 1013 (NCT657) at 17. Novo Nordisk is listed as the sponsor of the trial. *Id*. at 15.

87. The official title of NCT657 is "Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on

[3] I understand that Dr. Jusko and Dr. Bantle address the public availability of the clinicaltrials.gov website as of the priority date of the '462 patent. *See* Exs. 1003, 1005.

Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or Controlled With Diet and Exercise A 12 Week Multi-centre, Multi National, Double-blind, Placebo-controlled, Randomised, Nine Armed Parallel Group, Dose Finding Trial," with unique trial ID NN9535-1821. *Id.* at 15, 17. The Brief Summary section of NCT657 generally described the scope of the trial:

> This trial was conducted in Europe, Asia and Africa. Study 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). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

Id. at 15.

88. Six arms in the clinical trial (Experimental A-F) included 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. *Id.* at 15-16. A POSA would have understood the language "with titration," for the last two doses, to indicate that the recited dose amount was reached by starting from a lower dose amount and then stepping up periodically until reaching the final level.

89. The primary outcome measure followed in NCT657 was the level of HbA_{1c}, which refers to glycated hemoglobin, a long-term measure of mean plasma glucose concentrations. Ex. 1028 (Holst 2004) at 2. Some secondary outcome measures in NCT657 included the percentage of subjects with an adverse event or hypoglycemic episode, among others. NCT657 at 15.

90. Christine B. Jensen, MD, PhD, of Novo Nordisk A/S is listed as the study director for NCT657. *Id.* at 17. Christine Bjoern Jensen is listed at the named inventor on the '462 patent. Ex. 1001 ('462 patent) at 1.

D. Clinical Trial No. NCT00851773 (NCT773) (Ex. 1014)

91. *Safety, Tolerability, and Profile of Action of Drug in the Body of NN9535 in Healthy Male Japanese and Caucasian Subjects*, NCT00851773 ("NCT773"), is a clinical trial whose description was made available and listed on clinicaltrials.gov.[4] According to the face of NCT773, certain of its details were first submitted on February 25, 2009. Ex. 1014 (NCT773) at 9. Novo Nordisk is listed as the sponsor of the trial. *Id*. at 7.

[4] I understand that Dr. Jusko and Dr. Bantle address the public availability of the clinicaltrials.gov website as of the priority date of the '462 patent. *See* Exs. 1003, 1005.

92. The official title of NCT773 is "A Randomised, Double Blind, Placebo-controlled, Parallel-group, Multiple Doses, Dose Escalation Study to Assess the Safety, Tolerability, and Pharmacokinetics Profiles of NN9535 in Healthy Male Japanese and Caucasian Subjects After Weekly Subcutaneous Injections," with unique trial ID NN9535-3633. *Id* at 7, 9. The Brief Summary section of NCT773 generally described the scope of the trial:

> This trial is conducted in Europe. The aim of this clinical trial is to assess and compare the safety and tolerability, as assessed by adverse events after multiple subcutaneous doses of NN9535 in healthy male Japanese and Caucasian subjects.

Id. at 7.

93. Five arms in the clinical trial (Experimental A-E) included subcutaneous dosing of semaglutide, once weekly, at doses of 0.1, 0.2, and 0.4 mg (experimental arms A-C, respectively), a stepwise increase in doses from 0.4 for one week and then to 0.8 mg (experimental arm D), and a stepwise increase in doses from 0.4 for one week, to 0.8 mg for one week, and then to 1.2 mg (experimental arm E). *Id.* A POSA would have understood the stepwise increases in experimental arms D and E to be titrations, in which the final recited dose amount was reached by starting from a lower dose amount and then stepping up periodically until reaching the final level.

94. The primary outcome measure followed in NCT773 was the incidence of adverse events at each scheduled visit. *Id*. Some secondary outcome measures in NCT773 included the percentage of subjects with an adverse event or hypoglycemic episode, among others. *Id*.

E. WO 2006/097537 ("WO537") (Ex. 1015)

95. International Patent Application Publication Number No. WO 2006/097537 A2, entitled "Acylated GLP-1 Compounds," published on September 21, 2006. Ex. 1015 (WO537) at 1. WO537 identifies Novo Nordisk A/S as the applicant and the inventors as Jesper Lau, Florencio Zaragoza Dörwald, Henrik Stephensen, Paw Bloch, Thomas Kruse Hansen, and Kjeld Madsen. *Id.*

96. WO537 disclosed "[p]rotracted GLP-1 compounds and therapeutic uses thereof." *Id.* at 1, 2:5-6 ("This invention relates to the field of therapeutic peptides, i.e. to new protracted GLP-1 compounds."); *see also id.* at 5:1-3 ("The term 'GLP-1 peptide' as used herein means GLP-1 (7-37) (SEQ ID No 1), a GLP-1 (7-37) analogue, a GLP-1 (7-37) derivative or a derivative of a GLP-1 (7-37) analogue. In one embodiment the GLP-1 peptide is an insulinotropic agent."). WO537 disclosed the structure of semaglutide. Ex. 1057 (WO328) at 2:16-17; Ex. 1061 ('321 application) at [0010]; Ex. 1015 (WO537) at 48:4-8, 73:17-75:10.

97. WO537 disclosed that its GLP-1 compounds, including semaglutide, could be used in pharmaceutical formulations, combined 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." Ex. 1015 (WO537) at 6:32-35.

98. WO537 further disclosed 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." *Id.* at 25:11-16.

99. WO537 disclosed that because the GLP-1 agonist formulation could include excipients, it would include "chemical compounds which are normally added to pharmaceutical compositions, e.g. buffers, tonicity agents, preservatives and the like." *Id.* at 6:27-29.

100. WO537 disclosed exemplary pH ranges for a semaglutide 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 25:30–26:2.

101. WO537 also disclosed exemplary buffers for a semaglutide 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 26:4-8.

102. WO537 further disclosed that its GLP-1 agonists, which included semaglutide, could be used for once-weekly dosing: "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.

103. WO537 disclosed "[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 . . . ." *Id.* at 26:11-13. WO537 further disclosed that in "an embodiment the isotonicity agent is propylene glycol." *Id.* at 26:34-35. Further, a specific example is provided of a pharmaceutical formulation comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15. *Id.* at 64:10-15.

104. WO537 also disclosed that such "compositions are useful in formulation of parenteral controlled release and sustained release systems." *Id.* at 34:35–35:2. WO537 further disclosed 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 35:15-16; *see also id.* at 35:3-4 ("Even more preferably, are controlled release and sustained release systems administered subcutaneous.").

F. Lovshin (Ex. 1012)

105. Lovshin and Drucker, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009), was published in May 2009.

106. Lovshin disclosed that incretin-based drugs, like GLP-1 receptor agonists, were "routinely used to treat type 2 diabetes." Ex. 1012 (Lovshin) at 1.

107. Lovshin also disclosed 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.* Lovshin noted that because native GLP-1 has a short half-life in the body, degradation-resistant GLP-1 receptor agonists administered by subcutaneous injection were developed. *Id*. at 2.

108. Among the new GLP-1 agonists, Lovshin identified "NN9535," which a POSA would have known is semaglutide. *See* Ex. 1060 (WO193) at 35:18 ("semaglutide/NN9535 (Novo Nordisk"); *see also* Ex. 1013 (NCT657) at 15, 19 (update to NCT657 changing name of study title to refer to "semaglutide" rather than "NN9535"). Lovshin disclosed that NN9535 (semaglutide) treatment was being investigated at "0.1-1.6 mg once weekly" doses as an incretin therapy. Ex. 1012 (Lovshin) at 2 (Table 1).

109. Lovshin characterized NN9535 (semaglutide) as a "long-acting GLP-1R agonists" being studied; in particular, that it was one of "multiple once-weekly GLP-1 therapies … under active clinical investigation in phase I–II studies." *Id.* at 5.

G. Other Art That Informs the POSA's Knowledge

1. Lund (Ex. 1035)

110. Lund et al., *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011), published in 2011.

111. Lund is a review article discussing type-2 diabetes treatment by once daily, twice daily, and once weekly administration of several GLP-1 agonists:

GLP-1 receptor agonists for sc injection			
GLP-1-based		Exendin-4-based	
Daily	Weekly	Daily	Weekly
Liraglutide	Albiglutide	Exenatide	Exenatide-LAR
	Dulaglutide	Lixisenatide	CJC-1134-PC
	Semaglutide		

Ex. 1035 (Lund) at 3.

Compound	Company	Formulation	Status of development	Ongoing trials
Exenatide	Eli Lilly/Amylin Pharmaceuticals, Inc.	Twice-daily	Launched	Combination with insulin/ obesity + CVD
Liraglutide	Novo Nordisk	Once-daily	Launched	Combination with insulin/ obesity + CVD
Exenatide once-weekly	Eli Lilly/Amylin Pharmaceutical, Inc./ Alkermes, Inc.	Once-weekly	Expected 2011	Combination with insulin/ obesity
Lixisenatide	Zealand Pharma A/S/Sanofi-Aventis	Once-daily	Expected 2011	Phase III, GetGoal
CJC-1134-PC	ConjuChem	Once-weekly	Phase I/II	Phase I/II
Albiglutide	GlaxoSmithKline	Once-weekly	Expected 2012	Phase III, Harmony
Dulaglutide (LY2189265)	Eli Lilly	Once-weekly	Expected 2013	Phase III, Award
Semaglutide (NN9535)	Novo Nordisk	Once-weekly	Phase II	On hold

Id. at 4 (Table 1).

112. Lund disclosed that "[s]emaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly s.c. injections, based on the GLP-1 backbone, in preparation by Novo Nordisk." *Id.* at 7.

113. Lund further disclosed that "three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657). At the end of March 2011, a Phase I study looking at the influence of the pharmacokinetics of an oral contraceptive combination drug after administration of semaglutide was initiated (NCT01324505)." *Id.* at 7-8.

114. I understand that Lund was published before the earliest possible priority date of the '462 patent, but that it was published within one year following

the earliest possible priority date. If the Board disagrees that Lund is prior art, all my opinions are the same.

2. U.S. Patent No. 7,022,674 ("'674 patent") (Ex. 1075)

115. U.S. Patent No. 7,022,674 ("'674 patent") is titled "Polypeptide Compositions with Improved Stability" and was issued on April 4, 2006, from U.S. Patent Application 10/130,836, which is a U.S. National Stage Application filed under 35 U.S.C. § 371 from International Application No. PCT/US00/32421, filed December 5, 2000, and published as WO 01/43762 ("WO762") on June 21, 2001, which claims the benefit of U.S. Provisional Application 60/171,135, filed December 16, 1999, and U.S. Provisional Application No. 60/181,030, filed February 8, 2000.

116. The '674 patent is directed to "novel preparations of polypeptide compositions for parenteral administration comprising glycerin that have improved chemical stability compared to polypeptide compositions previously known." Ex. 1075 ('674 patent) at 5:39-43. The '674 patent disclosed a "preferred group of polypeptides for incorporation into the compositions of the present invention consists of . . . derivatives of GLP-1." *Id.* at 11:10-27.

117. The '674 patent disclosed "[o]ther excipients, such as isotonicity agents in addition to glycerin, preservatives, protamine, buffers, solubilizers, detergents, antioxidants, solution stabilizers and metal cations may be used in the compositions

of the present invention according to formulations conventionally used for polypeptides." *Id*. at 19:55-60. The '674 patent disclosed glycerin as an isotonicity agent. *Id*. at 1:40-43.

118. The '674 patent provided many examples of various polypeptide formulations with an isotonic agent, buffer, and preservative. For example, Example 25 disclosed 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, 7 mM sodium phosphate, and 3.2 mg/ml m-cresol at a pH of about 7.9. *Id.* at 33:27-43.

119. Example 32 of the '674 patent disclosed a solution containing liraglutide at a pH of 8.0. *Id*. at 35:1-14. The example disclosed that 10 mg of Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-GLP1(7-37)OH was dissolved in 5 ml of 0.01 N NaOH followed by the addition of 20 mg of m-cresol and 160 mg of glycerin derived from propylene. *Id*. at 35:6-9. The '674 patent further disclosed "[t]he solution is adjusted to pH 8.0 and diluted to 10 mL total volume with water." *Id.* at 35:9-11. "Each mL of this polypeptide composition contains about 1 mg of Arg(34), N-ε-(γ-Glu(N-α-hexadecanoyl))-Lys(26)-GLP1(7-37)OH, about 16 mg of glycerin and about 2 mg of m-cresol." *Id.* at 35:11-14.

120. Example 28 provided a 1 mg/ml human leptin solution containing 16 mg/ml glycerin, 7 mM sodium phosphate, 3 mg/ml m-cresol and the pH is then adjusted to 8.0. *See id.* at 34:7-18.

3. U.S. Patent No. 6,458,924 ("'924 patent") (Ex. 1073)

121. U.S. Patent No. 6,458,924 ("'924 patent") is titled "Derivatives of GLP-1 Analogs," was filed on September 16, 1999, and issued on October 1, 2002, more than one year before the earliest priority date for the '462 patent. Novo Nordisk A/S is listed as the Assignee. Ex. 1073 ('924 patent) at (73). The inventors listed are Liselotte Bjerre Knudsen, Per Olaf Huusfeldt, and Per Franklin Nielsen. *Id.* at (75).

122. The '924 patent relates to pharmaceutical compositions comprising a GLP-1 derivative having a lipophilic substituent. *Id.* at Abstract. The '924 patent disclosed GLP-1 analogs. *See, e.g., id.* at 8:20-153:45, 173:20-47. The '924 patent provided formulations including GLP-1 derivatives, an isotonic agent, a buffer, and a preservative. *Id.* at 153:46-56, 201:11-204:34.

4. U.S. Patent No. 6,284,727 ("'727 patent") (Ex. 1071)

123. The '727 patent is titled "Prolonged Delivery of Peptides," and it issued on September 4, 2001.

124. The '727 patent taught the specific sequence of GLP-1(7-37) and that it was known to have insulinotropic activity. Ex. 1071 ('727 patent) at 1:25-37. The patent also taught that "certain derivatives [of GLP-1(7-37)] and the use thereof to treat Diabetes mellitus in a mammal" were known. *Id.* at 1:38-42. The '727 patent disclosed that derivatives of GLP-1 polypeptides, including GLP-1(7-37) (including variants having inconsequential amino acid substitutions) had insulinotropic

activity. *See*, *e.g.*, *id.* at 1:38-2:15, 15:3-6, 21-27. Furthermore, the '727 patent described "methods for the treatment of non-insulin dependent diabetes mellitus in a mammal comprising the prolonged administration of GLP-1 (7-37), and related peptides." *See*, *e.g.*, *id*. at Abstract, 2:52-59.

5. U.S. Patent No. 6,268,343 ("Knudsen patent") (Ex. 1034)

125. U.S. Patent No. 6,268,343 is titled "Derivatives of GLP-1 Analogs," and issued July 31, 2001, from U.S. Patent Application No. 09/258,750 filed February 26, 1999. Novo Nordisk A/S is listed as the assignee of the Knudsen patent. Ex. 1034 (Knudsen patent) at (73).

126. Knudsen patent disclosed "GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making an [sic] using same." *Id.* at Abstract. Knudsen patent stated "[i]t is a further object of the invention to provide a pharmaceutical composition with improved solubility and stability." *Id*. at 5:13-15.

127. Knudsen patent taught that "[p]referably, the pharmaceutical compositions comprise an isotonic agent, a preservative and a buffer. Examples of isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol. Suitable buffers include sodium acetate and sodium phosphate." *Id.* at 168:1-6.

128. Knudsen patent disclosed "pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g. as described in Remington's *Pharmaceutical Sciences*, 1985 or in Re[m]ington: *The Science and Practice of Pharmacy*, 19th edition, 1995." *Id.* at 169:24-28. Knudsen patent also disclosed "[f]or example, injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product." *Id*. at 169:29:33.

129. Knudsen patent also taught "[i]n a preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection." *Id.* at 169:38-40. "Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, e. g. a lyophilised product, which has to be dissolved in a solvent before it can be injected." *Id.* at 169:40-44.

6. U.S. Patent No. 5,512,549 ("'549 patent") (Ex. 1017)

130. The '549 patent is titled "Glucagon-Like Insulinotropic Peptide Analogs, Compositions, and Methods of Use." The '549 patent was published on April 30, 1996.

131. The '549 patent taught glucagon-like insulinotropic peptide (GLP-1(7-37)) analogs and derivatives. Ex. 1017 ('549 patent) at Abstract. The '549 patent

also taught that other GLP-1 variants and analogs were known in the prior art and were known to stimulate insulin secretion. *See id.* at 2:33-43. The '549 patent also disclosed that the GLP-1(7-37) derivatives may be used in "a method for treating non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising administering an effective amount of [the GLP-1 derivative]." *Id.* at 3:55-60; *see also id*. at Abstract, 1:9-11, 3:9-11, 9:48-52, 27:4-28:21.

7. U.S. Patent No. 5,164,366 ("'366 patent") (Ex. 1072)

132. U.S. Patent No. 5,164,366 ("'366 patent") is titled "Human Insulin Analogues," and was published on November 17, 1992.

133. The '366 patent provided preparations of solutions containing human insulin analogues. Ex. 1072 ('366 patent) at 7:64-8:10. The '366 patent described insulin preparations containing a pharmaceutically acceptable salt in an aqueous solution or suspension, preferably at a neutral pH. *Id.* at 7:64-8:3. The '366 patent further described that "[t]he aqueous medium is made isotonic, for example with sodium chloride, sodium acetate or glycerol." *Id.* at 8:3-5. The '366 patent provided additional components for the solution including "zinc ions, buffers such as acetate and citrate and preservatives such as m-cresol, methylparaben or phenol." *Id.* at 8:5-8. "The pH value of the preparation is adjusted to the desired value." *Id*. at 8:8-10. In Example IV of the '366 patent, an injectable formulation was prepared by dissolving a human insulin analogue in 4 mL of 0.1 M HCl and 20 mL of 1.5 % m-

cresol was added. *Id*. at 17:15-22. The '366 patent disclosed the solution was mixed with 40 mL of 4% glycerol and 20 mL of 65 mM disodium hydrogen phosphate. *Id.* at 17:18-20. The pH value was adjusted to 7.3 and water was added. *Id*. at 17:20-22.

8. U.S. Patent No. 5,118,666 ("'666 patent") (Ex. 1056)

134. The '666 patent is titled "Insulinotropic Hormone," which was granted on June 2, 1992.

135. The '666 patent described derivatives of glucagon-like peptide I (GLP-1), including GLP-1(7-37) and variants having amino acid substitutions. Ex. 1056 ('666 patent) at Abstract, 3:3-59, 5:15-6:19. The '666 patent also explained that "[i]t is possible to enhance the biological half-life of the GLP-1 (1-37) derivatives" by bonding the derivatives to a chemical moiety such as a lipid, carbohydrate, or amino acid residue. *Id.* at 8:43-55; *see also id*. at 6:33-36 ("The present invention concerns the GLP-1(1-37) derivatives which have an insulinotropic activity that exceeds the insulinotropic activity of either GLP-1(1-37) or GLP-1(1-36).").

9. Victoza label (Ex. 1039)

136. Victoza® was approved by FDA in 2010, and the first approved label describing its use issued in January 2010. Ex. 1039 (Victoza label) at 9.

137. According to the Victoza label, "Victoza is a glucagon-like peptide-1 (GLP-1) receptor agonist indicated as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus (1)." *Id.* at 2. "Victoza

contains liraglutide, an analog of human GLP-1" that "acts as a GLP-1 receptor agonist." *Id.* at 5.

138. 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." *Id.* at 2. The Victoza label listed the following inactive ingredients: "disodium phosphate dihydrate, 1.42 mg; propylene glycol, 14 mg; phenol, 5.5 mg; and water for injection." *Id.* at 5.

10. WO 03/002136 ("WO136") (Ex. 1041)

139. International Patent Application Publication No. WO 03/002136 ("WO136") is titled "Stable Formulation of Modified GLP-1," and was filed on June 27, 2002, and published on January 9, 2003. WO136 claims priority to six Danish applications filed between June 28, 2001, and January 18, 2002. Ex. 1041 (WO136) at (30). Novo Nordisk A/S is listed as an Applicant. *Id.* at (71). The named inventors are James M. Flink, Silke Moller Larsen, Simon Bjerregaard Jensen, and Dorthe Kot Engelund. *Id.* at (72).

140. WO136 described pharmaceutical formulations containing GLP-1 compounds that are physically and chemically stable at high concentrations, which are suitable for subcutaneous injection. *Id.* at 4:17-30. WO136 incorporated by reference multiple patent applications providing examples of suitable GLP-1

compounds. *See id.* at 24:10-12 (citing WO 98/08871, WO 99/43705, WO 99/43706, WO 99/43707, WO 99/43708, WO 99/43341).

141. WO136 explained that unlike small molecules, "proteins are sensitive to both chemical and physical degradation." *Id.* at 3:14-15. WO136 stated that "GLP-1 is known to be prone to instability due to aggregation" and that both chemical and physical "degradation pathways may ultimately lead to loss of biological activity of the protein drug." *Id.* at 3:18-20.

142. WO136 disclosed pharmaceutical formulations that may include "a GLP-1 compound, and a buffer," wherein "said formulation has a pH from 7.0 to 10." *Id.* at 4:32–5:14. WO136 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." *Id*. at 18:27-30. WO136 further described "glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, [and] sodium phosphate" as "preferred." *Id*. at 18:30-33.

143. WO136 disclosed that the pharmaceutical formulation may include an isotonic agent "selected from the group consisting of a salt (e.g. sodium chloride), a polyhydric alcohol (e.g. propyleneglycol, xylitol, mannitol, sorbitol or glycerol), a monosaccharide (e.g. glucose or maltose), a disccharide [sic] (e.g. sucrose), an amino acid (e.g. L-glycine, L-histidine, arginine, lysine, isoleucine, aspartic acid,

tryptophan, threonine), polyethyleneglycol (e.g. PEG400)." *Id.* at 19:34-20:4. WO136 stated throughout the disclosure that neither sodium chloride nor mannitol should be used as the isotonicity agent when the formulation has a pH of 7.4. *See, e.g.*, *id.* at 10:9-22. WO136 also taught that the pharmaceutical formulation includes other ingredients such as a preservative, an isotonic agent, a chelating agent, a stabilizer, and a surfactant, and provided examples which are provided as alternatives. *Id.* at 19:16–22:30. WO136 explained that the use of preservatives, isotonic agents, chelating agents, stabilizers, and surfactants was "well-known to the skilled person." *Id.* at 19:30-33, 20:17-19, 20:30-32, 21:24-26, 22:28-30.

11. WO 00/37098 ("WO098") (Ex. 1074)

144. International Patent Application Publication No. WO 00/37098 A1 ("WO098") is titled "Shelf-Stable Formulation of Glucagon-Like Peptide-1," was filed on December 21, 1999, and published June 29, 2000, well before the earliest priority date for the '462 patent. WO098 claims priority to U.S. Provisional Application No. 60/113,499, filed on December 22, 1998, prior to the earliest priority date for the '462 patent. Eli Lilly and Company is listed as the Applicant. Ex. 1074 (WO098) at (71). The inventors listed are Mark Brader and Allen Pekar. *Id.* at (75).

145. WO098 disclosed a "shelf stable formulation that comprises a therapeutically effective amount of GLP-1, a pharmaceutically acceptable

preservative, and a tonicity modifier, and that has a pH between about 8.2 to about 8.8." *Id.* at abstract. WO098 taught that "[t]he long-term stability of peptides, particularly GLP-1, as components of a pharmaceutical composition for administration to mammals, is questionable" and that "[s]uch a lack of stability adversely affects bioavailability." *Id.* at 3-4. WO098 disclosed shelf-stable formulations of a GLP-1 molecule, a preservative (including phenol), a tonicity modifier (including glycerol), and a buffer (including TRIS). *Id.* at 9-10.

12. Additional prior art and references

146. In addition to the references discussed throughout this declaration, I utilize the knowledge and expertise of a POSA. Also, in this declaration I cite to references in addition to those recited and summarized above, including to provide background on the state of the art at the priority date. All references, whether summarized above or not, that were publicly available prior to the priority date of the '462 patent are within the scope of the prior art.

IX. UNPATENTABILITY OF THE CLAIMS OF THE '462 PATENT

A. Grounds 3 and 5: Claims 4–10 of the '462 patent would have been obvious over WO421 considering the '424 publication or over NCT657 and NCT773 considering the '424 publication

147. In my opinion, claims 4–10 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3), or over NCT657 and NCT773 considering the '424 publication (Ground 5).

148. Because I am offering opinions related to pharmaceutical formulations only, my opinions related to Grounds 3 and 5 are essentially the same, so I offer them both below.

149. Below, I explain why the dependent limitations of claims 4-10 would have been obvious in view of these references, considering that Drs. Bantle and Jusko are offering opinions related to the obviousness of claims 1-3. In addition, I understand additional experts are offering opinions on behalf of Mylan related to the pharmacological, and medical aspects of the claims. As above, a POSA here would consult others with relevant expertise and/or work as a team.

150. As explained above, claims 4–10 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, such as sodium dihydrogen phosphate; and/or (4) with a pH in the range of 7.0-9.0, or at a pH of 7.4. *See* Section V.A.

151. As a threshold matter, as of the priority date of the '462 patent, POSAs had a direct roadmap laid out in the prior art to formulate semaglutide. Notably, the Victoza label specified the components of the liraglutide formulation. Ex. 1039 (Victoza label) at 5. In particular, the label stated that Victoza was a solution for subcutaneous injection (*id.* at 2) and that it included disodium phosphate dihydrate,

propylene glycol, phenol, and water. *Id.* at 5. POSAs also knew that the liraglutide peptide and semaglutide peptide were very similar: the semaglutide peptide is different in only three respects when compared to liraglutide peptide. *See* ¶ 53.

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

152. First, as above, Victoza® was formulated as an aqueous solution, providing motivation and a reasonable expectation of success to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection. Ex. 1039 (Victoza label) at 2, 5

153. Moreover, 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, POSAs understood that parenteral dosage forms had several advantages in treating patients over non-parenteral formulations. Ex. 1069 (Remington) at 36-37. 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. Ex. 1069 (Remington) at 36-37; Ex. 1070 (Modern Pharmaceutics) at 7-10. 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. Ex.

1069 (Remington) at 36-37; *see also* Ex. 1071 ('727 patent) 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). POSAs 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. Ex. 1069 (Remington) at 36-37; *see also* Ex. 1035 (Lund) at 7-8 (disclosing "studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773)" and a "randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide"); Ex. 1013 (NCT657) at 7-8 (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).

154. 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. Ex. 1069 (Remington) at 37. Moreover, subcutaneous injections are convenient, allowing for patient self-administration. *Id.*

155. It was also well-known as of the priority date that GLP-1 compounds had problems with solubility and stability. *See, e.g.,* Ex. 1074 (WO098) at 3-4.

Therefore, POSAs sought to optimise GLP-1 compound formulations to provide improved soluble and stable formulations. *See, e.g.*, Ex. 1034 (Knudsen patent) at 5:13-15; Ex. 1074 (WO098) at 7 ("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."); Ex. 1075 ('674 patent) 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.").

156. POSAs were aware that vehicles provide a liquid carrier for the drug in parenteral formulations and are necessary for most parenteral delivery routes. Ex. 1069 (Remington) at 39-41. 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.*; Ex. 1070 (Modern Pharmaceutics) at 23; *see also* Ex. 1072 ('366 patent) 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").

157. 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. Ex. 1069 (Remington) at 36-37; Ex. 1070 (Modern Pharmaceutics) at 43-45.

158. WO421 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." Ex. 1011 (WO421) at 2:4-7. WO421 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 34:20-22 (emphasis added).

159. Similarly, NCT657 and NCT773 disclosed clinical trials studying subcutaneous dosing of semaglutide, once weekly, at doses of (1) 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively (NCT657); and (2) 0.1, 0.2, and 0.4 mg; a stepwise increase in doses from 0.4 for one week and then to 0.8 mg; and a stepwise increase in doses from 0.4 for one week, to 0.8 mg for one week, and then to 1.2 mg (NCT773). Ex. 1013 (NCT657) at 15-16 (investigating the 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); Ex. 1014 (NCT773) at 7 (a randomised, double blind, placebo-controlled, parallel-group, multiple doses, dose escalation study to assess the safety, tolerability, and pharmacokinetics profiles of semaglutide in male subjects after weekly subcutaneous injections). Additionally, the '424 publication disclosed that "[t]he inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known." Ex. 1016 ('424 publication) at [0003]. A POSA would have known that semaglutide is a peptide. Ex. 1057 (WO328) at 2:16-17 (semaglutide is "a GLP-1 derivative … disclosed in Example 4 of WO 06/097537"); Ex. 1015 (WO537) at 48:5-9 (describing semaglutide as a "peptide" and disclosing its amino acid sequence).

160. Accordingly, in view of WO421 considering the '424 publication (Ground 3), or in view of NCT657 and NCT773 considering the '424 publication (Ground 5), 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.

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

161. Second, the Victoza® formulation also included propylene glycol and phenol, again providing POSAs motivation with a reasonable expectation of success of using the same with semaglutide. Ex. 1039 (Victoza label) at 5.

162. Again, this motivation and reasonable expectation of success using the prior art Victoza® formulation would have been informed by the wealth of the prior art within a POSAs knowledge. When formulating, POSAs would carefully consider how 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.

163. Because excipients can have profound effects on the performance of a drug, POSAs understood that it was important that parenteral preparations are "of the very best quality and provide the maximum safety for the patient." Ex. 1069 (Remington) at 37. 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. Ex. 1070 (Modern Pharmaceutics) at 18; Ex. 1069 (Remington) at 37-38.

164. Thus, POSAs 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.*, Ex. 1039 (Victoza label) at 2, 5 (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, POSAs knew that it would be preferable to minimize the number of excipients used in a parenteral dosage form. Ex. 1070 (Modern Pharmaceutics) at 18.

165. WO421 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." Ex. 1011 (WO421) at 40:23-26.

166. Similarly, NCT657 and NCT773 disclosed clinical trials studying subcutaneous dosing of semaglutide, once weekly, at doses of (1) 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively (NCT657); and (2) 0.1, 0.2, and 0.4 mg; a stepwise increase in doses from 0.4 for one week and then to 0.8 mg; and a stepwise increase in doses from 0.4 for one week, to 0.8 mg for one week, and then to 1.2 mg (NCT773). Ex. 1013 (NCT657) at 15-16 (investigating the 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); Ex. 1014 (NCT773) at 7 (a randomised, double blind, placebo-controlled, parallel-group, multiple doses, dose escalation study to assess the safety, tolerability, and pharmacokinetics profiles of semaglutide in male subjects after weekly subcutaneous injections).

167. The '424 publication 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." Ex. 1016 ('424 publication) at 13 (claim 1). Dependent claims recited that the peptide is GLP-1, *id.* at claim 12, or that the formulation included a disodium phosphate dihydrate buffer, *id.* at claim 10.

168. WO421 disclosed the use of propylene glycol (Ex. 1011 (WO421) at 38:35) and the '424 publication 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." Ex. 1016 ('424 publication) at claim 1. The '424 publication further disclosed the use of propylene glycol as an isotonicity agent in aqueous solutions containing GLP-1 agonists. *See id*. at claim 12, [0025] (the use of propylene glycol as an isotonicity agent).

169. The ’424 publication also disclosed that “[t]he use of a preservative in pharmaceutical compositions is well-known to the skilled person,” *id.* at [0117], and that “phenol (5.0 or 5.5 mg/ml)” is a preservative. *Id*. at [0117]. The ’424 publication further disclosed that “[i]n a preferred embodiment of the invention the preservative is phenol or m-cresol.” *Id*. at [0115].

170. The ’424 publication further disclosed that propylene glycol at certain concentrations in peptide formulations reduced deposits and clogging of injection devices. *Id*. at [0005]; *id.* at [0145] (“the ability of propylene glycol to reduce clogging of injection devices when compared to other isotonic agents and to mannitol in particular.”), *id.* at [0027] (“[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.”).

171. Accordingly, in view of WO421 considering the ’424 publication (Ground 3), or in view of NCT657 and NCT773 considering the ’424 publication (Ground 5), 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.

3. *A POSA would have been motivated to formulate semaglutide with a phosphate buffer, such as sodium dihydrogen phosphate, with a reasonable expectation of success*

172. Third, the Victoza® formulation also included the phosphate buffer, sodium dihydrogen phosphate, again providing POSAs with motivation and a reasonable expectation of success of using the same with semaglutide. Ex. 1039 (Victoza label) at 5.

173. Here, however, a POSA's significant formulation knowledge would also have informed this motivation and reasonable expectation of success. Indeed, POSAs were 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 (Ex. 1057 (WO328) at 12:31), 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. Ex. 1070 (Modern Pharmaceutics) at 22, 39; Ex. 1069 (Remington) at 20; *see also* Ex. 1073 ('924 patent) at 153:46-56, 201:11-204:34 (providing formulations including GLP-1 derivatives, an isotonic agent, a buffer, and a preservative).

174. POSAs were also aware of using phosphate as the buffer, such as sodium dihydrogen phosphate. WO136 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." Ex. 1041 (WO136) at 18:27-30; *see also* Ex. 1075 ('674 patent) 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). WO136 further described "glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, [and] sodium phosphate" as "preferred." Ex. 1041 (WO136) at 18:30-33.

175. WO421 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." Ex. 1011 (WO421) at :23-26.

176. Similarly, NCT657 and NCT773 disclosed clinical trials studying subcutaneous dosing of semaglutide, once weekly, at doses of (1) 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively (NCT657); and (2) 0.1, 0.2, and 0.4 mg; a stepwise increase in doses from 0.4 for one week and

then to 0.8 mg; and a stepwise increase in doses from 0.4 for one week, to 0.8 mg for one week, and then to 1.2 mg (NCT773). Ex. 1013 (NCT657) at 15-16 (investigating the 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); Ex. 1014 (NCT773) at 7 (a randomised, double blind, placebo-controlled, parallel-group, multiple doses, dose escalation study to assess the safety, tolerability, and pharmacokinetics profiles of semaglutide in male subjects after weekly subcutaneous injections).

177. The '424 publication 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." Ex. 1016 ('424 publication) at 13 (claim 1). Dependent claims recited that the formulation includes a disodium phosphate dihydrate buffer. *Id.* at claims 10-11. 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.

178. Examples 1-6 of the '424 publication (each exemplary formulation) disclosed the use of a phosphate buffer at a pH within the range of 7.0-9.0. *Id.* at [0180]-[0251].

179. The ’424 publication 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 [0114].

180. The ’424 publication’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 [0220]–[0249].

181. Accordingly, in view of WO421 considering the ’424 publication (Ground 3), or in view of NCT657 and NCT773 considering the ’424 publication (Ground 5), and in light of the state of the art, a POSA would have been motivated to formulate semaglutide with a phosphate buffer, such as sodium dihydrogen phosphate, with a reasonable expectation of success.

4. 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

182. Moreover, as of the priority date of the ’462 patent, POSAs were aware that careful consideration must be given to specific parameters, such as pH and tonicity, when developing the parenteral formulation to minimize potential adverse

effects of tissue damage and injection pain. Ex. 1070 (Modern Pharmaceutics) at 43-45. Because parenteral dosages are often intended for multiple dosing, POSAs would have been aware that anti-microbial excipients may be necessary in the formulation. Ex. 1069 (Remington) at 41. POSAs would also recognize 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.*; Ex. 1070 (Modern Pharmaceutics) at 7-10.

183. POSAs would be aware that extreme values of pH, such as 2.3 and 11, may result in tissue injury and cell death. Ex. 1070 (Modern Pharmaceutics) at 43-45. 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* Ex. 1069 (Remington) at 37; Ex. 1070 (Modern Pharmaceutics) at 43-45; *see also* Ex. 1075 ('674 patent) 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); Ex. 1072 ('366 patent) at 17:18-22 (disclosing a solution containing 40 mL of 4% glycerol and 20 mL of 65 mM disodium hydrogen phosphate, and the pH value was adjusted to 7.3 and water was added).

184. WO421 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." Ex. 1011 (WO421) at 40:23-26.

185. Similarly, NCT657 and NCT773 disclosed clinical trials studying subcutaneous dosing of semaglutide, once weekly, at doses of (1) 0.1, 0.2, 0.4, and 0.8 mg, and 0.8 mg with titration and 1.6 mg with titration, respectively (NCT657); and (2) 0.1, 0.2, and 0.4 mg; a stepwise increase in doses from 0.4 for one week and then to 0.8 mg; and a stepwise increase in doses from 0.4 for one week, to 0.8 mg for one week, and then to 1.2 mg (NCT773). Ex. 1013 (NCT657) at 15-16 (investigating the 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); Ex. 1014 (NCT773) at 7 (a randomised, double blind, placebo-controlled, parallel-group, multiple doses, dose escalation study to assess the safety, tolerability, and pharmacokinetics profiles of semaglutide in male subjects after weekly subcutaneous injections).

186. The '424 publication 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." Ex. 1016 ('424 publication) at 13 (claim 1).

187. Dependent claims in the ’424 publication claimed “[t]he formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.” *Id.* at claim 6. Examples 1-6 of the ’424 publication (each exemplary formulation) disclosed the use of a phosphate buffer at a pH within the range of 7.0-9.0. *Id.* at [0180]-[0251].

188. Example 3 of the ’424 publication disclosed using a formulation with a pH of “7.40, 7.70, 7.90, or 8.15.” *Id.* at [0219]. The ’424 publication’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 [0220]–[0249].

189. The ’424 publication 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 claim 1.

190. Accordingly, in view of WO421 considering the ’424 publication (Ground 3), or in view of NCT657 and NCT773 considering the ’424 publication (Ground 5) 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.

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

191. 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." Ex. 1001 ('462 patent) at 35:49-52. I understand that Drs. Bantle and Jusko have offered the opinion that the limitations of claim 1 would have obvious over WO421 considering the '424 publication or over NCT657 and NCT773 considering the '424 publication.

192. As detailed in Sections IX.A.1, IX.A.3, and IX.A.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 4.

193. Notably, WO421, the '424 publication, NCT657, and NCT773 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.*, Ex. 1011 (WO421) at 36:23-37:5, 44:13 (disclosing that semaglutide is administered "by subcutaneous injection (0.1-1.6 mg)" to treat type 2 diabetes); Ex. 1016 ('424 publication) at [0003] (disclosing that "[t]he inclusion of isotonicity agents in peptide-containing

pharmaceutical formulations is widely known"); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

194. 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 (Ex. 1057 (WO328) at 12:31), 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.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (in aqueous solutions containing GLP-1 agonists, using disodium phosphate dihydrate as a "preferred" buffer); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

195. 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.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (disclosing GLP-1 agonist formulations with a pH within the range of 7.0-9.0, and specifically at 7.40); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

196. Accordingly, claim 4 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

6. The dependent limitations of claim 5 would have been obvious

197. Claim 5 depends from claim 4 and recites the additional limitation "wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 35:53-54. I explain that the limitations of claim 4 would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5). *See* Section IX.A.5.

198. As detailed in Section IX.A.2, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 5.

199. Notably, WO421, the '424 publication, NCT657, and NCT773 taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1011 (WO421) at 38:35, 40:23-26 (using propylene glycol as an excipient in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at claims 1, 23, [0216] (in aqueous solutions containing GLP-1 agonists, using propylene glycol as an isotonicity agent and phenol as a "preferred"

preservative); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

200. Accordingly, claim 5 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

7. The dependent limitations of claim 6 would have been obvious

201. Claim 6 depends from claim 4 and recites the additional limitation "wherein the pH is 7.4." Ex. 1001 ('462 patent) at 36:40-41. I explain that the limitations of claim 4 would have been obvious over WO421 considering the '424 publication (Ground 3), or over NCT657 and NCT773 considering the '424 publication (Ground 5). *See* Section IX.A.5.

202. As detailed in Section IX.A.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 6.

203. Notably, WO421, the '424 publication, NCT657, and NCT773 taught POSAs to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (disclosing GLP-1 agonist formulations with a pH

within the range of 7.0-9.0, and specifically at 7.40); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

204. Accordingly, claim 6 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

8. The dependent limitations of claim 7 would have been obvious

205. Claim 7 depends from claim 6 and recites the additional limitation "wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 36:42-43. I explain that the limitations of claim 6 would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5). *See* Section IX.A.7.

206. As detailed in Section IX.A.2, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 7.

207. Notably, WO421, the '424 publication, NCT657, and NCT773 taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1011 (WO421) at 38:35, 40:23-26 (using propylene glycol as an excipient in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1017 ('424 publication) at claims 1, 23, [0216] (in aqueous solutions containing GLP-1

agonists with a pH of from about 7.0 to 10.0, using propylene glycol as an isotonicity agent and phenol as a "preferred" preservative); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

208. Accordingly, claim 7 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

9. The dependent limitations of claim 8 would have been obvious

209. Claim 8 depends from claim 4 and recites the additional limitation "wherein the phosphate buffer is a sodium dihydrogen phosphate buffer." Ex. 1001 ('462 patent) at 36:44-45. I explain that the limitations of claim 4 would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5). *See* Section IX.A.4.

210. As detailed in Section IX.A.3, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 8.

211. Notably, WO421, the '424 publication, NCT657, and NCT773 taught POSAs that the addition of a sodium dihydrogen phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4 (Ex. 1057 (WO328) at 12:31), 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.*,

Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (in aqueous solutions containing GLP-1 agonists, using disodium phosphate dihydrate as a "preferred" buffer); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

212. Accordingly, claim 8 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

10. The dependent limitations of claim 9 would have been obvious

213. Claim 9 depends from claim 1 and recites the additional limitations "wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 36:46-51. I understand that Drs. Bantle and Jusko have offered the opinion that the limitations of claim 1 would have obvious over WO421 considering the '424 publication or over NCT657 and NCT773 considering the '424 publication.

214. As detailed in Sections IX.A.1-IX.A.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitations recited in claim 9.

215. Notably, WO421, the '424 publication, NCT657, and NCT773 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.*, Ex. 1011 (WO421) at 36:23-37:5, 44:13 (disclosing that semaglutide is administered "by subcutaneous injection (0.1-1.6 mg)" to treat type 2 diabetes); Ex. 1016 ('424 publication) at [0003] (disclosing that "[t]he inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known"); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

216. These references also taught POSAs that the addition of a sodium dihydrogen phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4 (Ex. 1057 (WO328) at 12:31), 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.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding

solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (in aqueous solutions containing GLP-1 agonists, using disodium phosphate dihydrate as a "preferred" buffer); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

217. 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.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (disclosing GLP-1 agonist formulations with a pH within the range of 7.0-9.0, and specifically at 7.40); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

218. These references also taught that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1011 (WO421) at 38:35, 40:23-26 (using propylene glycol as an excipient in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at claims 1, 23, [0216] (in aqueous solutions containing GLP-1 agonists, using propylene glycol as an isotonicity agent and phenol as a "preferred" preservative); Ex. 1013 (NCT657) at

15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

219. Accordingly, claim 9 of the '462 patent would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5).

11. The dependent limitations of claim 10 would have been obvious

220. Claim 10 depends from claim 9 and recites the additional limitation "wherein the pH is 7.4." Ex. 1001 ('462 patent) at 36:52-53. I explain that the limitations of claim 9 would have been obvious over WO421 considering the '424 publication (Ground 3) or over NCT657 and NCT773 considering the '424 publication (Ground 5). *See* Section IX.A.10.

221. As detailed in Section IX.A.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 10.

222. Notably, WO421, the '424 publication, NCT657, and NCT773 taught POSAs to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, Ex. 1011 (WO421) at 40:23-26 (using known additives in GLP-1 receptor agonist formulation "for aiding solubility or for preservation" to "obtain injectable solutions"); Ex. 1016 ('424 publication) at [0180]-[0251] (disclosing GLP-1 agonist formulations with a pH

within the range of 7.0-9.0, and specifically at 7.40); Ex. 1013 (NCT657) at 15-16 (subcutaneous once-weekly dosing of semaglutide); Ex. 1014 (NCT773) at 7 (same).

223. Accordingly, claim 10 of the ’462 patent would have been obvious over WO421 considering the ’424 publication (Ground 3) or over NCT657 and NCT773 considering the ’424 publication (Ground 5).

12. Conclusion

224. For each of claims 4–10 of the ’462 patent, a POSA would have been motivated to formulate the claimed semaglutide into a subcutaneous injection formulation as an isotonic aqueous solution, including a phosphate buffer at a pH in the range of 7.0-9.0. The prior art disclosed semaglutide formulation pH ranges that overlap with the claimed pH values recited in the dependent claims of the ’462 patent. And a POSA would have had a reasonable expectation of success of making such a formulation using conventional techniques known to a POSA. My opinions are limited to the formulation elements in claims 4–10 of the ’462 patent. However, I understand it is Dr. Bantle’s opinion that WO537 disclosed all treatment-related elements of claims 4–10 of the ’462 patent. Thus, claims 4–10 of the ’462 patent would have been obvious over WO421 considering the ’424 publication (Ground 3) or over NCT657 and NCT773 considering the ’424 publication (Ground 5).

B. Ground 4: Claims 4–10 of the '462 patent would have been obvious over WO537 considering Lovshin

225. In my opinion, claims 4–10 of the '462 patent would have been obvious over WO537 considering Lovshin. Below, I explain why the challenged claims would have been obvious in view of these references. In addition, I understand additional experts are offering opinions on behalf of Mylan related to the pharmacological, and medical aspects of the challenged claims, which are consistent with my opinions below. As above, a POSA here would consult others with relevant expertise and/or work as a team.

226. As explained above, claims 4–10 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, such as sodium dihydrogen phosphate; and/or (4) with a pH in the range of 7.0-9.0, or at a pH of 7.4. *See* Section V.A.

227. As with Grounds 3 and 5, hereto, as of the priority date of the '462 patent, POSAs had a direct roadmap laid out in the prior art to formulate semaglutide. Notably, the Victoza label specified the components of the liraglutide formulation. Ex. 1039 (Victoza label) at 5. In particular, the label stated that Victoza was a solution for subcutaneous injection (*id.* at 2) and that it includes disodium

phosphate dihydrate, propylene glycol, phenol and water. *Id*. at 5. POSAs also knew that the liraglutide peptide and semaglutide peptide were very similar: the semaglutide peptide is different in only three respects when compared to liraglutide peptide. *See* ¶ 53.

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

228. First, as above, Victoza® was formulated as an aqueous solution, providing motivation and a reasonable expectation of success. Ex. 1039 (Victoza label) at 2, 5.

229. Moreover, this motivation and reasonable expectation of success using the prior art Victoza® formulation would have been informed by the wealth of the prior art within a POSAs knowledge. In particular, a POSA as of the priority date of the '462 patent would have been motivated to formulate semaglutide as an isotonic aqueous solution for subcutaneous injection with a reasonable expectation of success. *See* Section IX.A.1.

230. WO537 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." Ex. 1015 (WO537) at 23:24-29, 33:32-33. Example 4 of WO537 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 23:24-26.

231. WO537 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 39:3-4. WO537 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 WO537 disclosed once-weekly administration of GLP-1 peptides, including semaglutide. *Id.* at 60:24-25.

232. WO537 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 35:15-16; *see also id.* at 35:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

233. Adding to WO537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide, as a POSA would have been known, *see* Ex. 1035 (Lund) at 4), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Ex. 1012 (Lovshin) at 2. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

234. Accordingly, in view of WO537 considering Lovshin, 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.

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

235. Second, the Victoza® formulation also included propylene glycol and phenol, again providing POSAs motivation with a reasonable expectation of success of using the same with semaglutide. Ex. 1039 (Victoza label) at 5.

236. Again, this motivation and reasonable expectation of success using the prior art Victoza® formulation would have been informed by the wealth of the prior art within a POSAs knowledge. As of the priority date of the '462 patent, POSAs would have been motivated to formulate semaglutide with propylene glycol and phenol with a reasonable expectation of success. *See* Section IX.A.2.

237. WO537 provided a specific example of a pharmaceutical formulation comprising semaglutide, propylene glycol, phenol, and a phosphate buffer, where the pH is 8.15. Ex. 1015 (WO537) at 64:10-15.

238. WO537 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 26:11-13. WO537 also disclosed that in "an embodiment the isotonicity agent is propyleneglycol." *Id.* at 26:34-35. Further, WO537 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 64:10-15; *see also* Ex. 1016 ('424 publication) at [0205]–[0214] (disclosing a formulation with a pH of 7.4).

239. Adding to WO537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide, as a POSA would have been known, *see* Ex. 1035 (Lund) at 4), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Ex. 1012 (Lovshin) at 2. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

240. Accordingly, in view of WO537 considering Lovshin, 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.

3. A POSA would have been motivated to formulate semaglutide with a phosphate buffer, such as sodium dihydrogen phosphate, with a reasonable expectation of success

241. Third, 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. Ex. 1039 (Victoza label) at 5.

242. Again, as explained above, a POSA as of the priority date of the '462 patent would have been motivated to formulate semaglutide with a phosphate buffer, such as sodium dihydrogen phosphate, with a reasonable expectation of success. *See* Section IX.A.3.

243. WO537 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." Ex. 1015 (WO537) at 6:32-35.

244. WO537 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 25:11-16.

245. WO537 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 26:4-8.

246. Adding to WO537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide, as a POSA would have been known, *see* Ex. 1035 (Lund) at 4), was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Ex. 1012 (Lovshin) at 2. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

247. Accordingly, in view of WO537 considering Lovshin, and in light of the state of the art, a POSA would have been motivated to formulate semaglutide with a phosphate buffer, such as sodium dihydrogen phosphate, with a reasonable expectation of success.

4. 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

248. As explained above, 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.A.4.

249. WO537 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." Ex. 1015 (WO537) at 6:32-35.

250. WO537 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 25:11-16.

251. WO537 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 25:30-26:2.

252. Adding to WO537, Lovshin 2009 disclosed that NN9535 (i.e., semaglutide, as a POSA would have been known, *see* Ex. 1035 (Lund) at 4, was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Ex. 1012 (Lovshin) at 2. It would have been routine to a POSA to optimize the formulation to contain a 1.0 mg dose of semaglutide.

253. Accordingly, in view of WO537 considering Lovshin, 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.

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

254. 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." Ex. 1001 ('462 patent) at 35:49-52. I understand that Drs. Bantle and Jusko have offered the opinion that the limitations of claim 1 would have obvious over WO537 considering Lovshin.

255. As detailed in Sections IX.A.1, IX.A.3, and IX.A.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 4.

256. Notably, WO537 and Lovshin 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.*, Ex. 1015 (WO537) at 35:3-16 (disclosing that semaglutide is preferably administered subcutaneously by a pen-like syringe); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

257. 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 (Ex. 1057 (WO328) at 12:31), 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.*, Ex. 1015 (WO537) at 26:4-8 (in an aqueous GLP-1 compound formulation, such as semaglutide, using disodium phosphate dihydrate as an exemplary buffer); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

258. 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.*, Ex. 1015 (WO537) at 25:11-26:2 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

259. Accordingly, claim 4 of the '462 patent would have been obvious in view of WO537 considering Lovshin.

6. The dependent limitations of claim 5 would have been obvious

260. Claim 5 depends from claim 4 and recites the additional limitation "wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 35:53-54. I explain that the limitations of claim 4 would have been obvious over WO537 considering Lovshin. *See* Section IX.B.5.

261. As detailed in Section IX.B.2, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 5.

262. Notably, WO537 and Lovshin taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1015 (WO537) at 26:11-35, 64:10-15 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

263. Accordingly, claim 5 of the ’462 patent would have been obvious in view of WO537 considering Lovshin.

7. The dependent limitations of claim 6 would have been obvious

264. Claim 6 depends from claim 4 and recites the additional limitation “wherein the pH is 7.4.” Ex. 1001 (’462 patent) at 36:40-41. I explain that the limitations of claim 4 would have been obvious over WO537 considering Lovshin. *See* Section IX.B.5.

265. As detailed in Section IX.B.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 6.

266. Notably, WO537 and Lovshin taught POSAs to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, Ex. 1015 (WO537) at 25:11-26:2 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

267. Accordingly, claim 6 of the ’462 patent would have been obvious in view of WO537 considering Lovshin.

8. The dependent limitations of claim 7 would have been obvious

268. Claim 7 depends from claim 6 and recites the additional limitation "wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 36:42-43. I explain that the limitations of claim 6 would have been obvious over WO537 considering Lovshin. *See* Section IX.B.7.

269. As detailed in Section IX.B.2, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 7.

270. Notably, WO537 and Lovshin taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1015 (WO537) at 26:11-35, 64:10-15 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

271. Accordingly, claim 7 of the '462 patent would have been obvious in view of WO537 considering Lovshin.

9. The dependent limitations of claim 8 would have been obvious

272. Claim 8 depends from claim 4 and recites the additional limitation "wherein the phosphate buffer is a sodium dihydrogen phosphate buffer." Ex. 1001 ('462 patent) at 36:44-45. I explain that the limitations of claim 4 would have been obvious over WO537 considering Lovshin. *See* Section IX.B.5.

273. As detailed in Section IX.B.3, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 8.

274. Notably, WO537 and Lovshin taught POSAs that the addition of a sodium dihydrogen phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4 (Ex. 1057 (WO328) at 12:31), 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.*, Ex. 1015 (WO537) at 26:4-8 (in an aqueous GLP-1 compound formulation, such as semaglutide, using disodium phosphate dihydrate as an exemplary buffer); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

275. Accordingly, claim 8 of the '462 patent would have been obvious in view of WO537 considering Lovshin.

10. The dependent limitations of claim 9 would have been obvious

276. Claim 9 depends from claim 1 and recites the additional limitations "wherein the semaglutide is administered by subcutaneous injection in the form of an isotonic aqueous solution comprising at a sodium dihydrogen phosphate buffer at a pH in the range of 7.0-9.0, and wherein the solution further comprises propylene glycol and phenol." Ex. 1001 ('462 patent) at 36:46-51. I understand that Drs. Bantle and Jusko have offered the opinion that the limitations of claim 1 would have obvious over WO537 considering Lovshin.

277. As detailed in Section IX.B.1-IX.B.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitations recited in claim 9.

278. Notably, WO537 and Lovshin 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.*, Ex. 1015 (WO537) at 35:3-16 (disclosing that semaglutide is preferably administered subcutaneously by a pen-like syringe); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

279. These references also taught POSAs that the addition of a sodium dihydrogen phosphate buffer in a semaglutide solution would (1) preserve a physiological pH, which is about pH 7.4 (Ex. 1057 (WO328) at 12:31), 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.*, Ex. 1015 (WO537) at 26:4-8 (in an aqueous GLP-1 compound formulation, such as semaglutide, using disodium phosphate dihydrate as an exemplary buffer); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

280. 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.*, Ex. 1015 (WO537) at 25:11-26:2 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

281. These references also taught POSAs that the addition of propylene glycol and phenol in a semaglutide solution would stabilize the formulation. *See, e.g.*, Ex. 1015 (WO537) at 26:11-35, 64:10-15 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

282. Accordingly, claim 9 of the '462 patent would have been obvious in view of WO537 considering Lovshin.

11. The dependent limitations of claim 10 would have been obvious

283. Claim 10 depends from claim 9 and recites the additional limitation "wherein the pH is 7.4." Ex. 1001 ('462 patent) at 36:52-53. I explain that the limitations of claim 9 would have been obvious over WO537 considering Lovshin. *See* Section IX.B.10.

284. As detailed in Section IX.B.4, a POSA would have been motivated to formulate, with a reasonable expectation of success, the additional limitation recited in claim 10.

285. Notably, WO537 and Lovshin taught POSAs to formulate semaglutide with a pH of 7.4 to minimize potential adverse effects of tissue damage and injection pain. *See, e.g.*, Ex. 1015 (WO537) at 25:11-26:2 (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); Ex. 1012 (Lovshin) at 2 (disclosing that semaglutide was being investigated for once-weekly dosing in the 0.1-1.6 mg dose range).

286. Accordingly, claim 10 of the ’462 patent would have been obvious in view of WO537 considering Lovshin.

12. Conclusion

287. For each of claims 4–10 of the ’462 patent, a POSA would have been motivated to formulate the claimed semaglutide into a subcutaneous injection formulation as an isotonic aqueous solution, including a phosphate buffer at a pH in the range of 7.0-9.0. The prior art disclosed semaglutide formulation pH ranges that overlap with the claimed pH values recited in the dependent claims of the ’462 patent. And a POSA would have had a reasonable expectation of success of making such a formulation using conventional techniques known to a POSA. My opinions are limited to the formulation elements in claims 4–10 of the ’462 patent. However, I understand it is Dr. Bantle’s opinion that WO537 disclosed all treatment-related elements of claims 4–10 of the ’462 patent. Thus, claims 4–10 of the ’462 patent would have been obvious over WO537 considering Lovshin.

C. No Secondary Considerations Overcome *Prima Facie* Obviousness

1. The formulations recited in the ’462 patent produce no unexpected results

288. I understand that, to show unexpected results, Patent Owner must prove that the alleged invention produced benefits that were unexpected over the closest prior art. Patent Owner may assert that the claimed formulations showed unexpected results. I disagree. The subject matter of the claims of the ’462 patent formulations

were disclosed, contemplated, and/or claimed in the prior art. *See, e.g.*, Sections IX.A–IX.B. The '462 patent presents no unexpected results from those formulations.

289. For all the reasons explained herein, a POSA in July 2012 would have expected to formulate the claimed semaglutide into a subcutaneous injection formulation as an isotonic aqueous solution, including a phosphate buffer at a pH in the range of 7.0-9.0. The prior art disclosed semaglutide formulation pH ranges that overlap with the claimed pH values recited in the dependent claims of the '462 patent. A POSA would have had a reasonable expectation of success of making such a formulation using conventional techniques of the pharmaceutical industry as taught in the '424 publication. *See* Ex. 1016 ('424 publication) at [0127].

2. There was no long-felt but unmet need for the formulations recited in the '462 patent

290. I understand that, to show long-felt but unmet need, Patent Owner must prove that the art long suffered from a problem to which the alleged invention offered a solution. To the extent Patent Owner asserts that the formulations claimed in the '462 patent satisfied a long-felt but unmet need, any need for such a formulation would have been met by formulations disclosed in the prior art.

291. For example, the prior art disclosed of GLP-1 receptor agonist formulations of exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide. *See, e.g.*, Ex. 1011 (WO421) at 34:20-22.

The prior art also disclosed that injectable formulations of GLP-1 receptor agonists can be prepared according to then-known formulation techniques, for example, by 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. *See, e.g.*, *id.* at 40:23-26.

292. Therefore, any long-felt but unmet need Patent Owner may allege was satisfied by the formulations disclosed in the prior art.

3. There was no praise of the formulations recited in the '462 patent

293. To the extent Patent Owner asserts that there is any evidence of praise in the industry for the formulations claimed in the '462 patent, I disagree. I am not aware of any praise by others in the field confirming that the formulation aspects of the '462 patent (*e.g.*, via subcutaneous injection, with propylene glycol and phenol, a phosphate buffer, and in a pH range of 7.0-9.0) is the reason a once-weekly, 1.0 mg semaglutide formulation was possible.

294. As explained above, the claimed formulation was expressly disclosed and/or contemplated by the prior art (for example, WO537, Lovshin, WO421, the '424 publication, NCT657, and/or NCT773), so any praise in the industry would not be a result of the formulation elements in the '462 patent.

4. There was no industry skepticism of the formulations recited in the '462 patent

295. To the extent Patent Owner asserts that there is any evidence of industry skepticism that the formulations claimed in the '462 patent would not work, I disagree. The claimed formulation was expressly disclosed and/or contemplated by the prior art (for example, WO537, Lovshin, WO421, the '424 publication, NCT657, and/or NCT773), so any skepticism would have to be directed to the specific results of using the formulation, which are inherent. Thus, even if Patent Owners could show that others considered alternative formulations to be superior to the GLP-1 agonist formulations disclosed in the prior art, it would not change the fact that the formulation was known in the prior art.

X. RESERVATION OF RIGHTS

296. I reserve the right to supplement and/or expand on the opinions I have set forth in this declaration based on the information I have reviewed and/or based on any additional information produced in discovery, modifications of the Board's claim construction, in response to any expert declarations submitted on behalf of Patent Owner, or any other circumstances that may impact my opinions.

297. Moreover, at trial I may rely upon documents and/or other materials produced in this litigation, publicly available documents, and/or any documents the parties have exchanged, such as discovery responses. Additionally, I may rely on

visual aids and/or demonstrative exhibits that I prepare or have been prepared on my behalf based upon my opinions.

I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: By:

Dr. Paul Dalby

EXHIBIT A

EXHIBIT A

Exhibit No.	Description
1001	U.S. Patent No. 10,335,462
1002	U.S. Patent No. 10,335,462 file history excerpts
1011	WO 2011/138421
1012	Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)
1013	Clinical Trial No. NCT00696657
1014	Clinical Trial No. NCT00851773
1015	WO 2006/097537
1016	U.S. Patent Application Pub. No. US2007/0010424
1017	U.S. Patent No. 5,512,549
1028	Holst, *Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus*, 4 CURRENT OP. IN PHARMACOLOGY 589 (2004)
1034	U.S. Patent No. 6,268,343 ("Knudsen patent")
1035	Lund, *Emerging GLP-1Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)
1039	*Victoza*, PHYSICIANS' DESK REFERENCE (65th ed. 2010)
1041	WO 03/002136
1056	U.S. Patent No. 5,118,666
1061	U.S. Patent App. Pub. No. 2011/0166321
1069	REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)

Exhibit No.	Description
1070	Boylan, *Parenteral Products*, *in* MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)
1071	U.S. Patent No. 6,284,727
1072	U.S. Patent No. 5,164,366
1073	U.S. Patent No. 6,458,924
1074	WO 00/37098
1075	U.S. Patent No. 7,022,674
1081	Ozempic prescribing information (Oct. 2022)