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 JOHN BANTLE, M.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 Application Pub. No. US2011/0166321	’321 publication
U.S. Patent Application Pub. No. US2007/0010424	’424 publication (Ex. 1016)
U.S. Patent No. 10,335,462	’462 patent (Ex. 1001)
U.S. Patent No. 10,335,462 file history excerpts	’462 file history (Ex. 1002)
U.S. Patent No. 5,512,549	’549 patent
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Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)	Bell
Highlights of Prescribing Information: Bydureon, Revised: 01/2012	Bydureon label
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Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)	Drab
Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003)	Drucker 2003
Drucker, *The Incretin System: Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes*, 368 LANCET 1696 (2006)	Drucker 2006
Glaesner, *Engineering and Characterization of the Long-Acting Glucagon-Like Peptide-1 Analogue LY2189265, an Fc Fusion Protein*, 26 DIABETES/ METABOLISM RSCH. & REV. 287 (2010)	Glaesner

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Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)	Holst 1987
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)	Holst 2004
Jimenez-Solem, *Dulaglutide, a Long-Acting GLP-1 Analog Fused with an Fc Antibody Fragment for the Potential Treatment of Type 2 Diabetes*, 12 CURRENT OP. IN MOLECULAR THERAPEUTICS 790 (2010)	Jimenez-Solem
Kim, *Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects with Type 2 Diabetes*, 30 DIABETES CARE 1487 (2007)	Kim
Kirillova, *Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?*, 7(6) PLOS ONE 1 (2012)	Kirillova
Knudsen, *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26 DRUGS OF THE FUTURE 677 (2001)	Knudsen 2001
Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEMISTRY 4128 (2004)	Knudsen 2004
Knudsen, *Liraglutide, a GLP-1 Analogue to Treat Diabetes* in ANALOGUE-BASED DRUG DISCOVERY II (Fischer & Ganellin eds. 2010)	Knudsen 2010

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Full Name of Cited Reference	Abbreviation
U.S. Patent No. 6,268,343	Knudsen patent
Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REV. ENDOCRINOLOGY 262 (2009)	Lovshin (Ex. 1012)
Lund, *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OP. ON EMERGING DRUGS 607 (2011)	Lund
Mojsov, *Insulinotropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLIN. INVEST. 616 (1987)	Mojsov
Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)	Monami
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Clinical Trial No. NCT00696657	NCT657 (Ex. 1013)
Clinical Trial No. NCT00851773	NCT773 (Ex. 1014)
Nielsen, *Pharmacology of Exenatide (Synthetic Exendin-4): A Potential Therapeutic for Improved Glycemic Control of Type 2 Diabetes*, 117 REGUL. PEPTIDES 77 (2004)	Nielsen
Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)	Seino

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Victoza, PHYSICIANS' DESK REFERENCE (65th ed. 2010)	Victoza label
Vilsbøll, *Glucagon-Like Peptide-1 and Diabetes Treatment*, 21 INTERNATIONAL DIABETES MONITOR 1 (2009).	Vilsbøll
International Patent Application Pub. No. WO 03/002136	WO136
International Patent Application Pub. No. WO 2011/073328	WO328
International Patent Application Pub. No. WO 2011/138421	WO421 (Ex. 1011)
International Patent Application Publication No. WO 91/11457	WO457
International Patent Application Pub. No. WO 2006/097537	WO537 (Ex. 1015)
Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364 NEW ENGL. J. MED. 852 (2011)	Zarin

1. My name is John P. Bantle, M.D. I have been retained by Mylan Pharmaceuticals Inc. ("Mylan") to provide my expert opinions regarding the unpatentability of the claims 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 am a medical endocrinologist and Professor Emeritus of Medicine in the Division of Endocrinology and Diabetes, Department of Medicine, at the University of Minnesota. I have substantial experience in clinical research, treatment of patients, and academic publications in the field of the treatment of diabetes and related conditions.

3. I earned a Bachelor of Science degree in 1970 from the University of Minnesota and a Doctor of Medicine degree in 1972 from the University of Minnesota Medical School. I completed an internship at Cleveland Metropolitan General Hospital in 1973; residencies in internal medicine at the Mayo Clinic in Rochester, Minnesota, and Dunedin Public Hospital in Dunedin, New Zealand, in

1975 and 1976, respectively; and a fellowship in endocrinology and metabolism at the University of Minnesota in 1978. I was a long-time medical practitioner in Minnesota, and earned board certifications from the American Board of Internal Medicine and in Endocrinology and Metabolism.

4. For nearly 40 years, I was an instructor, assistant professor, associate professor, and then full professor, in the Department of Medicine of the University of Minnesota Medical School. Since 2017, I have held the position of Professor Emeritus at the medical school. I also held significant administrative and research positions: I was the Associate Director of the General Clinical Research Center at the University of Minnesota Medical School from 1983-2009, the Medical Staff Clinical Service Chief for Internal Medicine at Fairview-University Medical Center from 2001-2007, and the Clinical Research Implementation Services Leader of the Clinical and Translational Science Institute at the University of Minnesota from 2011-2013. Finally, I was the Interim Director and then the full Director of the Division of Endocrinology and Diabetes in the Department of Medicine at the University of Minnesota Medical School from 2008 to 2015.

5. I participated in numerous clinical trials, both as principal investigator and co-investigator, and remained current on treatment methods for patients with diabetes, including developing nutritional recommendations for people with diabetes and developing the national standards of care for diabetes patients.

6. I have authored approximately 120 publications and book chapters, and made numerous presentations on the topic of diabetes at national and international medical meetings.

7. I have received numerous honors and awards for my teaching, clinical excellence, and treatment of patients. For example, I was selected by my peers to be named by the Best Doctors Organization as one of the Best Doctors in America for twenty-two consecutive years from 1996-2017; I was named a Top Doctor by Minneapolis/St. Paul Magazine in 1992, 1994, 1996, 1999-2002, 2004, and 2006-2017; and I received the University of Minnesota Department of Medicine Clinical Excellence Award in 2002, 2004, and 2011.

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

- *Boehringer Ingelheim Pharms. Inc. v. Mankind Pharma Ltd.*, No. 18-cv-01689 (D. Del.);
- *BTG Int'l, Ltd. v Amneal Pharms. LLC, Amerigen Pharms., Inc., Teva Pharms. USA, Inc.,* Nos. 15-cv-5909, 16-cv-2449 and 17-cv-6435 (D.N.J.);
- *Janssen, Inc., Janssen Oncology, Inc. and BTG Int'l LTD v. Dr. Reddy's Labs. Ltd., Dr. Reddy's Labs., Inc. and Pharmascience, Inc.*, T-978-19 (Ottawa, Ontario); and
- *Novo Nordisk Inc. v. Mylan Institutional LLC*, No. 19-cv-01551 (D. Del.).

9. My qualifications are further described on my *curriculum vitae*, attached as Exhibit 1004.

B. Basis for Opinions and Materials Considered

10. 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

11. Mylan retained me as a technical expert to provide various opinions about the ’462 patent. I am being compensated at a rate of $400 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

12. My opinions are limited to the treatment of diabetes with semaglutide, as claimed in the ’462 patent. I present my opinions from the perspective of a POSA who is a medical doctor.

13. Based on my view 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) Ground 1: WO421 anticipated claims 1-3 of the ’462 patent;

b) Ground 2: Lovshin anticipated claims 1-3 of the ’462 patent;

c) Ground 3: Claims 1–10 of the ’462 patent would have been obvious over WO421 in view of the ’424 publication;

d) Ground 4: Claims 1–10 of the ’462 patent would have been obvious over WO537 in view of Lovshin; and

e) Ground 5: Claims 1–10 of the ’462 patent would have been obvious over NCT657 in view of NCT773 and further in view of the ’424 publication.

14. As detailed below, WO421 disclosed all the limitations recited in claims 1–3 of the ’462 patent.

15. However, to the extent the Board disagrees and finds that WO421 did not anticipate claims 1–3 of the ’462 patent, then, in light of the state of the art, WO421 would have motivated a skilled artisan to treat diabetes with a once weekly, 1.0 mg semaglutide injectable formulation with a reasonable expectation of success in doing so, rendering obvious claims 1–10 of the ’462 patent, alone or in view of the ’424 publication.

16. Additionally, both WO537 in view of Lovshin, and NCT657 in view of NCT773 and further in view of the ’424 publication would have motivated a skilled artisan to treat diabetes with a once weekly, 1.0 mg semaglutide injectable formulation with a reasonable expectation of success in doing so, in both cases rendering obvious claims 1–10 of the ’462 patent.

17. I understand that Mylan’s expert Dr. Paul Dalby is offering the opinion that it would have been obvious to a POSA to formulate semaglutide into an isotonic

aqueous solution having the various characteristics recited as limitations in dependent claims 4–10 of the ’462 patent.

18. I understand that Patent Owner may present expert opinions regarding “secondary considerations” of non-obviousness of the method of treatment claims, and/or of other 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

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

[1] As support for 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.

20. 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 the PTAB must find it more likely than not that the claims are unpatentable.

21. I understand that my opinions regarding unpatentability are presented 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.

22. 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.

23. 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.

24. 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

25. 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 the Board adopts, or the parties agree to, a different definition of a skilled artisan.

26. The subject matter of claims 1–10 of the ’462 patent falls within the medicinal chemical arts. A skilled artisan would have had (1) an M.D., a Pharm.D., or a 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, the skilled artisan would be (1) a highly skilled scientist lacking an M.D., a Pharm.D., or a 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, formulation, or administration of therapeutic agents, and the

literature concerning protein or peptide formulation and design, or diabetes treatments.

28. A skilled artisan would have understood the prior art references referred to herein and would have the capability to draw inferences. It is understood that, to the extent necessary, a skilled artisan may collaborate with one or more other skilled artisans for one or more aspects with which the other skilled artisan may have expertise, experience, and/or knowledge. Additionally, a skilled artisan could have had a lower level of formal education than what I describe here if the person has a higher degree of experience.

29. As explained in this declaration and exemplified by the information provided in my CV, I met the qualifications of a skilled artisan for purposes of the claims of the ’462 patent.

V. THE ’462 PATENT (EX. 1001) AND ITS CLAIMS

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

31. I have assumed that the earliest priority date to which the 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.” Therefore, I have been asked to assume that references pre-dating July 1,

2012, are prior art. To the extent Patent Owner later asserts and/or proves that the claims are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

A. The ’462 patent’s claims

32. 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.

33. Dependent claims 2–10 depend from claim 1, directly or indirectly, and are provided below.

34. Dependent claim 2 recites:

> 2. The method according to claim 1, wherein the semaglutide is administered by parenteral administration.

35. Dependent claim 3 recites:

> 3. The method according to claim 2, wherein the solution is administered by subcutaneous injection.

36. 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.

37. Dependent claim 5 recites:

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

38. Dependent claim 6 recites:

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

39. Dependent claim 7 recites:

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

40. Dependent claim 8 recites:

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

41. 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.

42. 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

43. 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 (File history) at 8.[2]

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[2] For all cited documents that are not an issued U.S. patent or published U.S. patent application publication, the cited page number refers to the branded page number of the exhibit and not, for example, to the internal page numbering of a journal article, book chapter, or international patent application publication.

44. The Examiner rejected the filed claims on July 23, 2018, for indefiniteness of claim language, anticipation in view of the prior art, and double patenting over U.S. Patent No. 9,764,003. *Id.* at 307-18. On the merits of the anticipation rejections, the Examiner asserted that NCT00696657, which disclosed the use of semaglutide and liraglutide, Madsbad, which disclosed the use of several GLP-1 agonists, and Kim, 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 (File history) at 312-15 (July 23, 2018 Office Action).

45. After these rejections, the applicants amended claim 1 to recite simply:

> 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.

See Ex. 1002 (File history) at 332.

46. Showing the relevant edits in full redline makes clear the extent of the applicants' changes:

> 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~~.

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

47. Following this amendment, the applicants filed a terminal disclaimer over U.S. Patent No. 9,764,003, which the Examiner characterized as claiming "a method for reducing body weight, comprising administering semaglutide once weekly in an amount of at least 0.7 mg and up to 1.6 mg to a subject in need thereof, wherein said semaglutide is administered without another therapeutic agent." *See* Ex. 1002 (File history) at 336 (February 28, 2019 Terminal disclaimer); *id.* at 317 (July 23, 2018 Office Action describing U.S. Patent No. 9,764,003).

48. 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 (File history) at 344-44 (March 6, 2019 Notice of Allowability).

49. The Examiner did not further consider the prior art or whether it would have anticipated or rendered obvious the amended claims. In particular, while the Examiner stated that NCT657 “does not teach or disclose” 1 mg semaglutide, the Examiner did not consider whether NCT657 rendered obvious that dose amount, alone or in combination with other references. The Examiner also appeared to consider it important that semaglutide “was used as [a]n add-on therapy,” but I understand this is not a relevant consideration in a claim like independent claim 1, which uses the transitional phrase “comprising,” meaning that use of semaglutide “as an add-on therapy” does not weigh in favor of novelty and nonobviousness.

50. Further, while the Examiner expressly mentioned NCT657 as being “[t]he closest prior art to the instant claims,” Ex. 1002 (File history) at 344, the

Examiner never considered that art in a substantive obviousness rejection against the issued claims.

51. Based on my review of the ’462 patent’s prosecution history, the Patent Office did not substantively apply the prior art described in my opinion against the issued claims of the ’462 patent. This includes WO421, WO537, NCT773, the ’424 publication, and Lovshin (2009), which together disclosed a once weekly, 1 mg dose of semaglutide to treat type 2 diabetes. *See* generally ’462 file history, including at 307-18 (July 13, 2018 Office action asserting rejections under 35 U.S.C. § 112; anticipation rejections over NCT657, Madsbad, and Kim; and obviousness-type double patenting over U.S. Patent No. 9,764,003); 341-46 (March 6, 2019 Notice of allowability withdrawing certain original rejections in view of claim amendments, and allowing claims to a 1 mg dose because in NCT00696657 “semaglutide or liraglutide was used as on add-on therapy” and “the reference does not teach or disclose a higher amount of 1 mg semaglutide”); and 347 (March 6, 2019 Examiner-Initiated Interview Summary confirming terminal disclaimer was needed to overcome rejection over U.S. Patent No. 9,764,003).

VI. CLAIM CONSTRUCTION

52. I understand that the claims that are the subject of this Petition for *inter partes* review are to be construed to have their plain and ordinary meaning as understood by a POSA considering the patent specification and prosecution file

history. I further understand that it is proper for patentees to act as their own lexicographers and define and use claim terms in ways specific to their patent.

53. Here, it is my opinion that no term in the claims of the ’462 patent needs construction to resolve the issue of unpatentability of those claims: in my opinion, under the plain and ordinary meanings of the claim terms as understood by a POSA, the claims are unpatentable.

54. Regarding the preamble of claim 1, I understand that the parties to the related district court litigation disagree whether the claim preamble is not a claim limitation and, if it is, its meaning.

55. Here, to the extent that the preamble is considered a claim limitation, it is my opinion that its plain and ordinary meaning is broad.

56. First, nothing in the words “method for treating type 2 diabetes” implicitly or explicitly limits, characterizes, or quantifies the outcome intended by the method, beyond the simple requirement for “treating.” A POSA would therefore understand the claim preamble broadly to encompass administering semaglutide for the purpose of alleviating or reducing the symptoms and complications associated with type 2 diabetes or otherwise managing the disease without requiring any specified treatment effect.

57. Second, this plain meaning is consistent with the specification of the ’462 patent, which broadly describes the concept of “treating” as:

> intended to include the full spectrum of treatments for a given condition from which the patient is suffering, such as administration of the active compound to alleviate the symptoms or complications; to delay the progression of the disease, disorder, or condition; to alleviate or relieve the symptoms and complications; and/or, to cure or eliminate the disease, disorder, or condition as well as to prevent the condition.

Ex. 1001 ('462 patent) at 5:20-27.

58. Thus, the '462 patent itself recognizes the broad plain and ordinary meaning of the preamble. However, to the extent the preamble is construed or understood to limit, characterize, or quantify the outcome intended by the method, such as by requiring a particular degree of effectiveness from the method, my opinions described in this declaration would remain the same: regardless of any degree of efficacy that may be required of the claims, the prior art provided a POSA with a motivation and reasonable expectation of success of practicing an effective method of treating type 2 diabetes with semaglutide, rendering the claims obvious, or anticipated them.

VII. BACKGROUND ON DIABETES AND THE USE OF GLP-1 DERIVATIVES FOR THE TREATMENT OF DIABETES

A. Diabetes Generally

59. Insulin is a hormone produced and secreted by the pancreatic islets, Ex. 1026 (Harrison's) at 6, which regulates the metabolism of blood sugar. Diabetes

mellitus, or simply "diabetes," is a metabolic disorder in which the body either fails to produce enough insulin or does not respond normally to insulin. Thus, diabetes is characterized by elevated, and sometimes abnormally and dangerously high, levels of glucose in the blood. *Id.* at 3.

60. There are three main types of diabetes: type 1, type 2, and gestational. *Id*. Type 1 diabetes, sometimes referred to as insulin-dependent diabetes, results from destruction of pancreatic beta cells and resulting insulin deficiency. *Id.* at 7. Type 2 diabetes, sometimes referred to as *non*-insulin dependent diabetes, involves both insulin resistance, which leads to an ineffective use of insulin by the body, and abnormal insulin secretion, leaving the levels of insulin inadequate to overcome the resistance. *Id.* at 8. The result is high blood glucose levels. Finally, gestational diabetes affects pregnant women and is often caused by insulin resistance. *Id.* at 4.

61. Diabetes is diagnosed by measuring a patient's blood glucose levels, testing glucose tolerance, and/or watching for signs and symptoms of diabetes. *Id.* at 5. Thus, diabetes may be diagnosed if the patient has a) symptoms of diabetes plus random blood glucose ≥11.1 mmol/L (200 mg/dL); or b) fasting plasma glucose ≥7.0 mmol/L (126 mg/dL); or c) two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test. *Id.* at 5, Table 338-2. If diabetes is not treated, the metabolic dysregulation can cause pathophysiologic changes in multiple organ systems, resulting in such medical problems as retinopathy, which may lead to

blindness, end-stage renal disease, and nontraumatic lower extremity amputations; uncontrolled diabetes can also predispose a patient to cardiovascular disease. *Id.* at 3.

B. Diabetes Treatment

62. The goals when treating patients with type 1 or type 2 diabetes are to: 1) eliminate symptoms related to hyperglycemia (high blood glucose levels); 2) reduce or eliminate long-term complications (i.e., those affecting the eyes, kidneys, nervous system, and circulatory system); and 3) allowing the patient a lifestyle as close to normal as possible. Ex. 1026 (Harrison's) at 22. To reach these goals, lowering plasma glucose is a primary aim. *Id.*

63. In 1922, Dr. Fredrick Banting and Charles Best discovered that insulin was secreted by the pancreas. Ex. 1018 (Banting). After isolating insulin, they found that it could be effective in the treatment of diabetes. *Id*. Specifically, insulin is a key mediator of glucose lowering and either administering exogenous insulin or stimulating the body's insulin production will lower blood glucose levels. Thus, beginning in the 1920s, patients diagnosed with diabetes could be treated with insulin injections. For patients with type 1 diabetes, an important goal is designing and implementing an insulin treatment regimen that mimics physiologic insulin secretion. Ex. 1026 (Harrison's) at 24.

64. In 1983, two peptides related to the hormone glucagon were found in the gut, and were named glucagon-like peptide 1 ("GLP-1") and glucagon-like peptide 2 ("GLP-2"). *See generally* Ex. 1019 (Bell). Additional studies discovered that the body naturally synthesizes truncated forms of the GLP-1 peptide, including GLP-1 (7-37). *See, e.g.*, Ex. 1036 (Mojsov); Ex. 1027 (Holst 1987). GLP-1 (7-37) was found to have an insulinotropic (stimulating insulin secretion) effect while also inhibiting the secretion of glucagon, a hormone that raises blood glucose. Ex. 1036 (Mojsov) at 1-3; Ex. 1027 (Holst 1987) at 4-6. A POSA therefore would have known since the 1980s that GLP-1 and certain of its truncated forms (e.g., GLP-1 (7-37)) were potential therapeutic agents for the treatment of diseases such as type 2 diabetes because of their ability to stimulate insulin, inhibit glucagon, and ultimately lower blood glucose levels.

65. As of the priority date of the '462 patent, in addition to traditional lifestyle modifications like improved diet and increased exercise, there were several classes of glucose-lowering therapies available to treat type 2 diabetics. The avenues for medical intervention typically fell into two categories: oral and parenteral. Ex. 1026 (Harrison's) at 27, Table 338-11. In the former category, a medical practitioner would most commonly choose from among biguanides, α-glucosidase inhibitors, dipeptidyl peptidase IV (DPP-4) inhibitors, insulin secretagogues, and thiazolidinediones. *Id*.

66. The mechanisms of action of the various oral diabetes treatments are summarized below:

Oral-Therapy Class	Example	Mechanism (e.g.)
Biguanides	Metformin	Lower liver glucose production
α-glucosidase inhibitors	Acarbose	Lower gut glucose absorption
DPP-4 inhibitors	Sitagliptin	Prolong GLP-1 action
Sulfonylurea secretagogues	Glyburide	Stimulate insulin secretion
Non-sulfonylurea secretagogues	Repaglinide	Stimulate insulin secretion
Thiazolidinediones	Pioglitazone	Lower insulin resistance

See id. at 27-28, Tables 338-11, -12.

67. In the category of parenteral medications, a medical practitioner would most commonly choose from among various insulin formulations, GLP-1 agonists, and amylin agonists. *Id.* at 27, Table 338-11.

68. The mechanisms of action of the various parenteral diabetes treatments are summarized below:

Parenteral-Therapy Class	Example	Mechanism (e.g.)
Insulin	Insulin	Greater glucose utilization
GLP-1 agonist	Exenatide	Higher insulin, lower glucagon
Amylin agonist	Pramlintide	Higher insulin, lower resistance

See id.

C. The Use of GLP-1 Derivatives to Treat Diabetes

69. For almost 100 years before the priority date, it was known that gut hormones are responsible for insulin secretion. *See generally* Ex. 1018 (Banting).

And, researchers had long investigated hormones and other peptides derived from the gastrointestinal tract to develop treatments for endocrine disorders such as diabetes. Thus, the use of gut hormones for the treatment of diabetes was long considered a therapeutic option.

70. GLP-1 derivatives (including derivatives of GLP-1 (7-37)) were a stronger focus of development in the early and mid-1990s, and these derivatives possessed improved pharmacological properties. *See, e.g.*, Ex. 1017 ('549 patent) at Abstract, 1:9-11, 2:27-32, 3:9-11, 25-30; Ex. 1042 (WO457) at 4:24-29, 5:2-7. The literature repeatedly encouraged the use of these derivatives of GLP-1(7-37) for the treatment of diabetes. Ex. 1017 ('549 patent) at Abstract, 1:9-11, 3:9-11, 55-60; Ex. 1042 (WO457) at Abstract.

71. "Type 2 diabetes is characterized by insulin resistance, impaired glucose-induced insulin secretion and inappropriately regulated glucagon secretion, which in combination eventually result in hyperglycemia and in the longer term in microvascular and macrovascular complications affecting multiple organ systems." Ex. 1040 (Vilsbøll) at 1. Incretin hormones like GLP-1 and its analogs and derivatives counteract these outcomes through the "incretin effect," which "refers to the amplification of glucose-stimulated insulin secretion elicited by hormones secreted from the gastrointestinal tract." *Id*.

72. GLP-1 is a polypeptide of about 30 amino acids, produced in the intestinal epithelium from processing of the expressed glucagon gene. *Id*. The intact, active form of GLP-1 induces an insulin response when plasma glucose exceeds a concentration of 4 mM, with stronger inducement at higher plasma glucose levels, by binding to and activating the GLP-1 receptors on pancreatic β-cells. *Id.* at 2. GLP-1 has other beneficial effects for diabetic patients, including: 1) enhancing insulin biosynthesis and insulin gene expression, 2) providing trophic and protective effects to the β-cells (stimulating β-cell growth, proliferation and neogenesis, and reducing β-cell apoptosis), 3) inhibiting glucagon secretion (which, combined with the effect on insulin secretion, yields inhibited hepatic glucose production and contributes to lower plasma glucose), 4) inhibiting upper gastrointestinal motility and secretion, 5) increasing satiety leading to weight loss, and 6) providing beneficial effects on the cardiovascular system. *Id*.

D. Use of Liraglutide to Treat Diabetes

73. Research into the use of GLP-1 and its derivatives led eventually to FDA approval of several GLP-1 receptor agonists such as exenatide and liraglutide

to treat type 2 diabetes. *See* Ex. 1021 (Byetta label);[3] Ex. 1020 (Bydureon label);[4] Ex. 1039 (Victoza label).[5] A POSA would have known that liraglutide was the subject of numerous clinical studies and publications describing its effectiveness and was studied alone or alongside other diabetes therapies. *See, e.g.*, Ex. 1024 (Drucker 2006); Ex. 1035 (Lund); Ex. 1033 (Knudsen 2010); Ex. 1040 (Vilsbøll).

74. Liraglutide, approved by FDA under the trade name Victoza, is "an analog of human GLP-1 and acts as a GLP-1 receptor agonist." Ex. 1039 (Victoza label) at 5; *see also* Ex. 1040 (Vilsbøll) at 3 (liraglutide is based on the structure of human GLP-1 and has 97% sequence homology to it, but also includes an amino

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[3] Ex. 1021 (Byetta label) retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s25lbl.pdf (last accessed March 11, 2023).

[4] Ex. 1020 (Bydureon label) retrieved from https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s000lbledt.pdf (last accessed March 11, 2023).

[5] Byetta (exenatide) was first approved in 2005. Ex. 1021 (Byetta label) at 1. Bydureon (exenatide extended release) was first approved in 2012. Ex. 1020 (Bydureon label) at 1. Victoza (liraglutide) was first approved in 2010. Ex. 1039 (Victoza label) at 2.

acid substitution and an attachment of a C16 acyl chain, which allows the polypeptide to bind albumin to prevent renal elimination and degradation by DPP-4). Liraglutide was approved with the following indication:

> 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).

Ex. 1039 (Victoza label) at 2.

75. Liraglutide, as used in Victoza, was to be "[a]dminister[ed] once daily at any time of day, independently of meals," subcutaneously, and it had a half-life of about 11-13 hours. Ex. 1039 (Victoza label) at 2; Ex. 1040 (Vilsbøll) at 3. Victoza dosing was "[i]nitiate[d] at 0.6 mg per day for one week," but that "dose [was] intended to reduce gastrointestinal symptoms during initial titration, and *is not* effective for glycemic control." Ex. 1039 (Victoza label) at 2 (emphasis added.) After one week of dosing at 0.6 mg daily, the dose of Victoza was increased to 1.2 mg daily for long-term treatment, an amount that could be "increased to 1.8 mg" if the lower dose "[did] not result in acceptable glycemic control." *Id*.

76. Liraglutide, the active ingredient in Victoza, "is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on [a] lysine residue at position 26 of the peptide precursor." *Id.* at 5. Liraglutide's amino acid sequence, as depicted in the Victoza label, is:

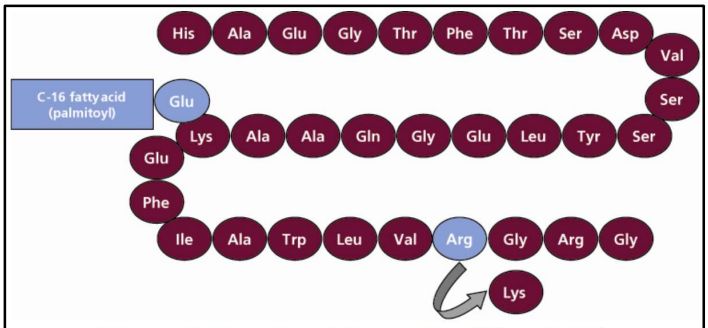


Figure 1 Structural Formula of liraglutide

Id.[6]

77. In single-letter abbreviation, the amino acid sequence of liraglutide, above, is:

HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

Id.

78. A POSA also would have known that semaglutide is a GLP-1 derivative receptor agonist and would have known its primary amino acid sequence. *See* Ex. 1061 ('321 publication) at [0010] ("WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk

[6] This figure appears in Ex. 1039. But for readability, I used the same figure from the electronic version of the Victoza label that appears on the Drugs@FDA website. That label is found at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf (last accessed March 11, 2023).

A/S."); Ex. 1015 (WO537) at 48:4-22 (Example 4). That amino acid sequence, in single-letter abbreviation is:

H[A]EGTFTSDVSSYLEGQAAKEFIAWLVRGRG

Ex. 1015 (WO537) at 48:4-22 (Example 4)(where "[A]" represents a modified amino acid).

79. Thus, a POSA would have known, as of the priority date, that liraglutide and semaglutide have nearly identical primary amino acid sequences, differing only at the modified [A] position in semaglutide, and were in the same therapeutic category of GLP-1 receptor agonists.

E. Extended-Use GLP-1 Receptor Agonists

80. Moving beyond daily-use GLP-1 receptor agonists like liraglutide, a POSA would have known, as of the priority date, of the development of various extended-use GLP-1 receptor agonists, i.e., GLP-1 receptor agonists that could be dosed less frequently than once or twice per day.

81. Lund, for example, disclosed a list of eight GLP-1-related compounds, or formulations of those compounds, being developed for use and in clinical trials: exenatide; liraglutide; lixisenatide; exenatide once weekly; CJC-1134-PC; albiglutide; dulaglutide (also known as LY2189265); and semaglutide (also known as NN9535). Ex. 1035 (Lund) at 4, Table 1. At least five of those eight compounds were identified as being developed for once weekly dosing:

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		

Id. at 3, Fig. 1;

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.

82. For each once weekly GLP-1 receptor agonist product listed in the table above as being expected for approval, a POSA would have known that the product would have been under development for several years before the application date for the ’462 patent, given the time required to complete the necessary clinical trials and studies.

83. Dulaglutide, as one example of a long-acting GLP-1 receptor agonist, is a GLP-1/immunoglobulin G (IgG4) Fc fusion protein. Ex. 1025 (Glaesner) at 1; Ex. 1029 (Jimenez-Solem) at 1. The half-life of dulaglutide after a single dose of 0.1 mg/kg was found in early studies to be approximately 1.5 days in rats and greater than 2 days in monkeys, with "a $t_{1/2}$ in humans of up to 90 h, making dulaglutide an ideal candidate for once-weekly dosing." Ex. 1025 (Glaesner) at 5; Ex. 1029 (Jimenez-Solem) at 1. Importantly, the dulaglutide fusion protein showed dose-dependent inducement of insulin release in response to glucose infusion in rats, enhancing secretion up to four-fold over placebo. Ex. 1025 (Glaesner) at 6; Ex. 1029 (Jimenez-Solem) at 2-3. Similarly, dulaglutide demonstrated at least a two-fold enhancement of glucose-elicited insulin release for at least 7 days in monkeys. Ex. 1025 (Glaesner) at 6-7. Finally, dosing in mice demonstrated durable reductions in plasma glucose and small but statistically significant weight reduction. Ex. 1025 (Glaesner) at 7. Each of these effects was demonstrated to be mediated by the GLP-1 receptor. Ex. 1025 (Glaesner) at 7; Ex. 1029 (Jimenez-Solem) at 3 ("The addition of the GLP-1 receptor antagonist exendin(9-39) (1 μM) to the medium reversed the effects of dulaglutide on insulin secretion."). Glaesner concluded that the results "support[ed] clinical development and investigation [of dulaglutide] as a potential long-lived GLP-1 receptor agonist for type 2 diabetes management." Ex. 1025 (Glaesner) at 9; *see also* Ex. 1029 (Jimenez-Solem) at 6 ("[T]he GLP-1-Fc fusion

protein dulaglutide is a new GLP-1 analog intended for once-weekly dosing with longer plasma residence than the native hormone.”).

84. Exenatide, as another example of a long-acting GLP-1 receptor agonist, is a synthetic version of exendin-4, a GLP-1 receptor agonist that is similar to, but different in sequence from, GLP-1, the molecules sharing 53% amino acid sequence overlap; i.e., exenatide is not a true GLP-1 analog. Ex. 1037 (Nielsen) at 1. Exendin-4, despite not being a GLP-1 analog, shares many of GLP-1’s glucoregulatory actions, including glucose-dependent enhancement of insulin secretion, glucose-dependent suppression of glucagon secretion, slowing of gastric emptying, reduction of food intake, and promotion of β-cell proliferation. *Id*. Not surprisingly, given these characteristics, the “GLP-1 receptor appears to be involved in, and necessary for, the incretin/insulinotropic actions of exenatide,” as it is for GLP-1. *Id.* at 3. Further, clinical trials on exenatide displayed “a consistent pattern of safety and pharmacodynamics,” including significant reductions in HbA1c.[7] *Id.* at 4-5. In addition, studies in humans showed that “subcutaneous exenatide (synthetic exendin-4) rapidly lowered both fasting and postprandial plasma glucose in patients with type 2 diabetes.” *Id.* at 5. Nielsen concluded by saying that, in the face of many

[7] The term “HbA_{1c}” refers to glycated hemoglobin, a long-term measure of mean plasma glucose concentrations. Ex. 1028 (Holst 2004) at 2.

positive effects from exenatide dosing, "[o]ngoing phase 3 clinical trials will reveal whether or not exenatide is proven safe and effective for the treatment of patients with type 2 diabetes." *Id.* at 10. As we now know, exenatide was found safe and effective and was approved by the FDA for marketing. Ex. 1035 (Lund) at 4, Table 1.

85. Regarding semaglutide specifically, Lund disclosed that "[s]emaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly [subcutaneous] injections, based on the GLP-1 backbone, in preparation by Novo Nordisk, Bagsværd, Copenhagen, Denmark." Ex. 1035 (Lund) at 7. Lund went on to say that multiple trials involving semaglutide were completed or in process before the filing date of the '462 patent:

> So far, 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.

86. Lund also noted that GLP-1 agonists had favorable effects on the cardiovascular system. In addition, he noted that "[t]he available GLP-1R agonists cause sustained weight loss and clinical [sic] relevant improvement of glycemic control. The long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects. Meta-analyses have shown promising effects on cardiovascular disease." *Id.* at 1.

87. Lund also disclosed the approval and benefits of liraglutide (Victoza):

> Liraglutide (Victoza®, Novo Nordisk, Bagsværd, Copenhagen, Denmark) is an acylated analog of human GLP-1 (with 97% homology with native GLP-1), which was approved for clinical use in Europe in 2009 and in the USA in 2010 (Table 1). In liraglutide, a C-16 acyl chain is linked to amino acid 20 via a γ-glutamic acid spacer and the lysine in position 28 of native GLP-1 is exchanged with arginine (Table 2) [41]. These changes results in a half-life in the range of approximately 11-15 h after s.c. administration [42], making it suitable for once-daily dosing [43].

Id. at 3.

88. Lund also noted the many benefits of liraglutide: lowered HbA_{1c} (a measure of blood glucose), lowered body weight, reduced fasting plasma glucose,

lower blood levels of triglycerides and free fatty acids, and decreased blood pressure. *Id.*

89. Lund also noted that a benefit of once weekly dosing, in development for several GLP-1 receptor agonists before the filing date of the '462 patent, was that it could "improve compliance, and … offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide)." *Id.* at 5. And, further, "that the longer-acting GLP-1R agonists have a more pronounced efficacy on glycemic control compared with the shorter-acting GLP-1R agonists, whereas the effect on body weight does not seem to differ significantly." *Id.* at 8.

90. Further, Lovshin disclosed a list of ten GLP-1-related compounds, or formulations of those compounds, being developed for use and in clinical trials: exenatide; liraglutide; AVA0010; exenatide once weekly; taspoglutide; albiglutide; CJC-1134-PC; NN9535 (semaglutide); dulaglutide (also known as LY2189265); and LY2428757. Ex. 1012 (Lovshin) at 2, Table 1. Seven of those ten compounds were being developed for once (or twice) weekly dosing. *Id.*:

Table 1 | Incretin-based therapies

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

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

91. In addition, Drab taught that "incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes." Ex. 1022 (Drab) at 1. Focusing on liraglutide specifically, Drab described the numerous clinical studies, including those in the Liraglutide Effect and Action in Diabetes (LEAD) program of phase III studies, that were performed to investigate liraglutide's use as a monotherapy or in combination with other antidiabetic drugs. *Id.* at 9-10.

92. Drab further noted, as was known in the art, that "GLP-1 and therapies that activate GLP-1 receptors only stimulate increases in insulin secretion when

glucose levels are elevated and, as a result, carry a very low risk of hypoglycemia[.]" *Id.* at 3.

93. Drab also specifically discussed the characteristics and activities of liraglutide:

> [Liraglutide] is an analog of human GLP-1 with 97% primary amino acid sequence identity, but with a fatty acid side chain attached through a glutamic acid linker. This fatty acid structure enables reversible plasma albumin binding, which may contribute to the drug's partial resistance to DPP-4 degradation and its subsequent prolonged action.
>
> * * *
>
> Studies that investigated the pharmacokinetic profile of liraglutide have shown that it reaches peak plasma levels 9–12 hours after dosing by subcutaneous injection, with a subsequent mean elimination half-life of 11–15 hours. Steady state is reached after 3 days, and therapeutic plasma liraglutide concentrations are observed for up to 24 hours after a single injection. These characteristics make liraglutide compatible with once-daily administration, and it may be possible to choose the dosing time without regard to meals.
>
> * * *

> When liraglutide monotherapy was investigated in a subgroup of previously drug-naïve patients over 52 weeks, reductions in A1C seen within the first 8–12 weeks of trial start were still evident at the end of the trial (–1.6% with liraglutide 1.8 mg after 52 wks). Of these previously drug-naïve subjects, 62% had A1C levels less than 7.0% at the end of the trial.
>
> * * *
>
> As with exenatide, the most common adverse effect of liraglutide is nausea, which led to withdrawal in 1–9% of patients receiving the 1.8-mg dose during the LEAD program. During the LEAD trials, the frequency of nausea with liraglutide ranged from 10.5% when combined with a sulfonylurea to 40% with a thiazolidinedione. In comparison, the frequency of nausea and/or vomiting reported with metformin is approximately 25%. As with exenatide, nausea with liraglutide can be limited by gradual dosage titration.

Id. at 5, 10.

94. Lovshin disclosed the benefits of using liraglutide, as well: reduction in HbA1c, reduction in fasting plasma glucose, weight loss, and reduced blood pressure. Ex. 1012 (Lovshin) at 3.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

95. I identify below the prior art references supporting my expert opinions on unpatentability of claims 1–10 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 skilled artisan as of the relevant priority date.

96. The prior art disclosures identified in this expert report would have been understood by a skilled artisan 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 skilled artisan, 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.

97. For every item of prior art recited here, 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 skilled artisan at the time of invention, including, without limitation, the knowledge described generally in this report (i.e., without referring to a specific document).

A. Lovshin (Ex. 1012)

98. Lovshin and Drucker, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009) ("Lovshin"), was published in 2009. I understand that Lovshin is prior art to the claims of the '462 patent.

99. Lovshin disclosed that incretin-based drugs, like GLP-1 receptor agonists, were commonly used to treat type 2 diabetes:

> Incretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus. These agents regulate glucose metabolism through multiple mechanisms, their use is associated with low rates of hypoglycemia, and they either do not affect body weight (dipeptidyl peptidase 4 inhibitors), or promote weight loss (glucagon-like peptide-1 receptor agonists). The success of exenatide and sitagliptin, the first therapies in their respective drug classes to be based on incretins, has fostered the development of multiple new agents that are currently in late stages of clinical development or awaiting approval. This Review highlights our current understanding of the mechanisms of action of incretin-based drugs, with an emphasis on the emerging clinical profile of new agents.

Ex. 1012 (Lovshin) at 1.

100. Lovshin 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 HbA1c effectively, and also results in weight loss." *Id*. Lovshin noted that because native GLP-1 has a short half-life in the body ("shorter than 2 min *in vivo*"), it was necessary to develop degradation-resistant GLP-1 receptor agonists to be administered by subcutaneous injection. *Id.* at 2. Lovshin noted that these GLP-1 agonists "act on pancreatic islets to stimulate insulin secretion and inhibit glucagon secretion, [and] also inhibit gastric emptying and promote satiety, which leads to weight loss, as shown in clinical studies (Figure 1)." *Id*.

101. 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. 1035 (Lund) at 4, Table 1 ("Semaglutide (NN9535) Novo Nordisk"); Ex. 1057 (WO328) at 2:16-17 ("Semaglutide, a GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S, is disclosed in Example 4 of WO 06/097537."). 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).

102. Lovshin characterized NN9535 (semaglutide) as a "long-acting GLP-1R agonist[]" being studied; in particular, that it was one of "multiple once-weekly GLP-1 therapies … under active clinical investigation in phase I–II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1)," though Lovshin asserted that, at the time, "few data are available on the structure or efficacy of the[] molecules." *Id.* at 5; *compare, e.g.*, Ex. 1015 (WO537) at 48:4-8 (Example 4, showing the amino acid sequence and structure of semaglutide).

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

103. U.S. Patent Application Publication Number No. US2007/0010424 A1 ("'424 publication"), 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.* I understand that the '424 publication is prior art to the claims of the '462 patent.

104. The '424 publication disclosed "pharmaceutical formulations comprising a peptide and propylene glycol, … methods of preparing such formulations, and … 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.

105. 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].

106. The ’424 publication further clarified that an “analogue” is:

> a peptide wherein one or more amino acid residues of the parent peptide have been substituted by another amino acid residue and/or wherein one or more amino acid residues of the parent peptide have been deleted and/or wherein one or more amino acid residues have been added to the parent peptide. Such addition can take place either at the N-terminal end or at the C-terminal end of the parent peptide or both. Typically “an analogue” is a peptide wherein 6 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, more preferably a peptide wherein 3 or less amino acids have been substituted and/or added and/or deleted from the parent peptide, and most preferably, a peptide wherein one amino acid has been substituted and/or added and/or deleted from the parent peptide.

Id. at [0039].

107. And the ’424 publication clarified that a “derivative” is:

> a peptide or analogue thereof which is chemically modified by introducing an organic substituent e.g. ester, alkyl or lipophilic functionalities, on one or more amino acid residues of the peptide or analogue thereof.

Id. at [0040].

108. Among the GLP-1 peptides described by the ’424 publication as being encompassed within its invention, there are many derivatives and analogs, including with amino acid substitutions and with lipophilic groups attached. *See, e.g.*, *id.* at [0041]-[0062].

109. 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].

110. 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].

111. 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].

112. Further, the ’424 publication taught that the disclosed peptides, in a formulation, could be dosed in an effective amount to treat the condition for which the peptide was considered to be effective, and that a person of skill in the art could determine the appropriate dosage:

> Of course, it is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used in methods of treatment of diseases or conditions for which use of the peptide is indicated. One skilled in the art would understand that when used in such methods of treatment, the formulations would have to be administered in amount effective to treat the condition or disease for which the peptide was being administered where an “effective amount” or an “amount . . . effective” is understood to mean a dosage which is sufficient in order for the treatment of the patient with the disease or condition to be treated to be effective compared to treatment without the administered dosage. It is to be understood that “an effective amount” is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for

> consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, the condition or disease to be treated (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

Id. at [0147].

113. 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].

114. 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].

115. 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. WO 2006/097537 (Ex. 1015)

116. International Patent Application Publication No. WO 2006/097537 A2 (“WO537”), entitled “Acylated GLP-1 Compounds,” published on September 21,

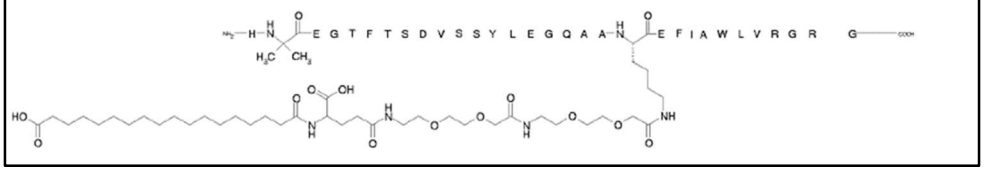
2006. Ex. 1015 (WO537) at 1. WO537 identified Novo Nordisk A/S as the applicant and the inventors as Jesper Lau, Florencio Zaragoza Dörwald, Henrik Stephensen, Paw Bloch, Thomas Kruse Hansen, and Kjeld Madsen. *Id.* I understand that WO537 is prior art to the claims of the ’462 patent.

117. WO537 disclosed “[p]rotracted GLP-1 compounds and therapeutic uses thereof. *Id.* at 1 (abstract), 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.”).

118. WO537 disclosed the structure of semaglutide in the specification and in Claim 28:

Example 4

N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



Ex. 1061 (’321 publication) at [0010]; Ex. 1015 (WO537) at 48:4-8, 73:17-75:10.

119. WO537 disclosed that there was a motivation to develop and use GLP-1 compounds that could be dosed less often than once daily: “Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily,

e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile." Ex. 1015 (WO537) at 2:31-33.

120. WO537 disclosed that its GLP-1 compounds, including semaglutide, could be used in pharmaceutical formulations, combined with excipients:

> The present invention also provides pharmaceutical compositions comprising a compound according to the present invention and the use of compounds according to the present invention for preparing medicaments for treating disease.

Id. at 3:6-8;

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

Id. at 6:32-35;

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

> surfactants. In one embodiment of the invention the pharmaceutical formulation is an aqueous formulation, i.e. formulation comprising water.

Id. at 25:11-16.

121. 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.

122. WO537 also disclosed that the prior art compound semaglutide, as one of the disclosed embodiments, could be used to prepare "a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, [or] obesity," or "for delaying or preventing disease progression in type 2 diabetes." *Id.* at 23:24–24:3.

123. WO537 also disclosed various features of an exemplary semaglutide formulation, such as its pH and various components that it may contain:

> 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.

> 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.

124. WO537 further disclosed that its described 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.

125. WO537 also disclosed "Pharmacokinetic Screening of Once Weekly GLP-1 Analogues":

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

Id. at 60:28-32.

126. WO537 also disclosed that semaglutide formulations could include "a pharmaceutically acceptable preservative," such as phenol, and an "isotonicity agent," like propylene glycol. *Id.* at 26:11-13, 34-35.

127. Following on this, WO537 disclosed a specific example of a pharmaceutical formulation with semaglutide, propylene glycol, phenol, and a phosphate buffer, all at pH 8.15:

Pharmaceutical formulation:	
A compound of the invention may be formulated as:	
Compound of example 4	6,25 mg/ml
Propyleneglycol	14,0 mg/ml
Phenol	5.5 mg/ml
Phosphate Buffer pH 8.15	

Id. at 64:10-15.

128. And of course, given its subject matter, WO537 disclosed that the semaglutide formulation could be administered parenterally, such as by

subcutaneous injection. *Id.* at 35:15-16 ("Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.").

129. WO537 also disclosed that the semaglutide formulation could be used to treat type 2 diabetes, among other conditions: "[i]n one embodiment a compound according to the invention is used for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, [or] obesity." *Id.* at 38:34-36.

D. WO 2011/138421 (Ex. 1011)

130. International Patent Application Publication No. WO 2011/138421 ("WO421"), entitled "Combination Therapy," published on November 10, 2011. Ex. 1011 (WO421) at 1. WO421 identified Boehringer Ingelheim International GMBH as the applicant and the inventors as Thomas Klein, Rolf Grempler, and Michael Mark. *Id.* I understand that WO421 is prior art to the claims of the '462 patent.

131. WO421 disclosed that a GLP-1 receptor agonist, like semaglutide, could be used as part of a method for treating type 2 diabetes:

> [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, to

> pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

Id. at 2:4-9.

132. WO421 acknowledged the variety of physical ailments that could be connected to a patient having type 2 diabetes:

> Type 2 diabetes mellitus is a common chronic and progressive disease arising from a complex pathophysiology involving the dual endocrine effects of insulin resistance and impaired insulin secretion with the consequence not meeting the required demands to maintain plasma glucose levels in the normal range. This leads to chronic hyperglycaemia and its associated micro- and macrovascular complications or chronic damages, such as e.g. diabetic nephropathy, retinopathy or neuropathy, or macrovascular (e.g. cardio- or cerebrovascular) complications. The vascular disease component plays a significant role, but is not the only factor in the spectrum of diabetes associated disorders. The high frequency of complications leads to a significant reduction of life expectancy. Diabetes is currently the most frequent cause of adult-onset loss of vision, renal failure, and amputation in the Industrialised World because of diabetes induced complications and is associated with a two to five fold increase in cardiovascular disease risk.

> Furthermore, diabetes (particularly type 2 diabetes) is often coexistent and interrelated with obesity and these two conditions together impose a particularly complex therapeutic challenge. Because of the effects of obesity on insulin resistance, weight loss and its maintainance [sic] is an important therapeutic objective in overweight or obese individuals with prediabetes, metabolic syndrome or diabetes. Studies have been demonstrated that weight reduction in subjects with type 2 diabetes is associated with descreased [sic] insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure. Maintainance [sic] of weight reduction over longer term is considered to improve glycemic control and prevent diabetic complications (e.g. reduction of risk for cardiovascular diseases or events). Thus, weight loss is recommended for all overweight or obese indivuduals [sic] who have or are at risk for diabetes. However, obese patients with type 2 diabetes have much greater difficulty losing weight and maintain the reduced weight than the general non-diabetic population.

Id. at 3:27-4:16.

133. WO421 also acknowledged that GLP-1 analogues were used as diabetes monotherapy, even though WO421 opened with a discussion of combination therapy: "Non-oral (typically injected) antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or

(initial or add-on) combination therapy) include, without being restricted thereto, GLP-1 or GLP-1 analogues, and insulin or insulin analogues." *Id.* at 6:19-21.

134. WO421 further disclosed "[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues)" that were described and disclosed in other prior art, including "exenatide, exenatide LAR [i.e., long-acting release formulation], liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide." *Id.* at 34:20-22.

135. WO421 also disclosed that GLP-1 receptor agonists, like semaglutide, could be formulated into injectable formulations:

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

Id. at 40:23-26.

136. In addition, WO421 disclosed that "[t]he GLP-1 receptor agonist is typically administered by subcutaneous injection, e.g. ranging from thrice daily, twice daily, once daily to once weekly injection. *Suitable doses and dosage forms of the GLP-1 receptor agonist may be determined by a person skilled in the art.*" *Id.* at 44:1-3 (emphasis added). WO421 noted that "[s]emaglutide," in particular, "is

administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13. This was in comparison to liraglutide, which "is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg)." *Id.* at 44:9-10.

137. Other once weekly dosage forms disclosed by WO421 included exenatide LAR, taspoglutide, albiglutide, and dulaglutide. *Id.* at 44:7-8, 11-12, 14-15, 18-19.

E. Semaglutide Clinical Trial Records

1. Clinical Trial No. NCT00696657 (Ex. 1013)

138. *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. According to the face of NCT657, certain of its details were first received by ClinicalTrials.gov on June 11, 2008. Ex. 1013 (NCT657) at 15. Novo Nordisk was listed as the sponsor of the trial. *Id.* I understand that NCT657 is prior art to the claims of the '462 patent.

139. 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 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. Ex. 1013 (NCT657) at 15, 17. The Brief Summary section of NCT657 generally describes 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.

140. 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, 0.8 mg with titration, and 1.6 mg with titration, respectively. Ex. 1013 (NCT657) 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. The arms do not indicate whether metformin or another treatment was continued during the trial. *Id.*

141. 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. 1013 (NCT657) at 15; 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. Ex. 1013 (NCT657) at 15.

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

2. Clinical Trial No. NCT00851773 (Ex. 1014)

143. *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.[8] 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

[8] https://clinicaltrials.gov/ct2/show/NCT00851773 (last accessed March 11, 2023). Consistent with the operation of clinicaltrials.gov, several versions of NCT773 were published and publicly available on ClinicalTrials.gov due to its regularly being updated by the trial sponsor, Novo Nordisk.

the sponsor of the trial. *Id.* at 8. I understand that NCT773 is prior art to the claims of the ’462 patent.

144. 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. Ex. 1014 (NCT773) at 7, 9. The Brief Summary section of NCT773 generally describes 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.

145. 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 for eight weeks (experimental arms A-C, respectively), a stepwise increase in doses from 0.4 for one week and then to 0.8 mg for seven weeks (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

for six weeks (experimental arm E). Ex. 1014 (NCT773) at 7.[9] 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.

146. The primary outcome measure followed in NCT773 was the incidence of adverse events at each scheduled visit. Ex. 1014 (NCT773) at 7. Some secondary outcome measures in NCT773 included the frequency of hypoglycemic episodes, patient vital signs, and antibody development against semaglutide, among others. *Id.*

3. ClinicalTrials.gov is a Part of the POSA's Knowledge

147. ClinicalTrials.gov is a website, maintained by the National Library of Medicine at the National Institutes of Health, that "provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions." Ex. 1076 (ClinicalTrials.gov Background) at 1.

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[9] NCT773 does not expressly recite the eight weeks of dosing for the 0.1, 0.2, and 0.4 mg doses, but a POSA would have known that, in the interest of gathering relevant results, the number of weeks those doses were administered would have to match the total number of weeks that the 0.8 (with titration) and 1.2 mg (with titration) dosing regimens were administered.

148. I understand that ClinicalTrials.gov was created by statute, as part of the Food and Drug Administration Modernization Act of 1997, in 42 U.S.C. § 282(i), and that the website became publicly accessible in February 2000. *See* Ex. 1076 (ClinicalTrials.gov Background) at 2. Clinicaltrials.gov was created under the Act "to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions," and it went live to the public in February 2000. Ex. 1076 (ClinicalTrials.gov Background) at 2.

149. ClinicalTrials.gov was highly successful in its effort to create this comprehensive, publicly-accessible resource. On January 1, 2004, Harvard's Kennedy School recognized ClinicalTrials.gov with the School's *Innovations in American Government* award. *See generally* Ex. 1077 (Harvard Award). According to the Kennedy School, ClinicalTrials.gov was especially deserving of the award because it addressed a pressing need in medical information management: "Not only were medical care providers unable to access information on clinical trials in an efficient manner, but patients were often unable to access it at all, depriving them of both information and the opportunity to seek experimental treatment through trial participation. In response, Congress passed the Food and Drug Modernization Act of 1997, mandating the creation of a centralized, publicly accessible registry for

federally and privately funded trials 'of experimental interventions for serious or life-threatening diseases and conditions.'" Ex. 1077 (Harvard Award) at 1-2.

150. As the School further noted in its award announcement, Clinicaltrials.gov is accessible, valuable, and relied upon because it presents information about clinical trials in a database that is readily searched and easily understandable:

> The site was also designed to be as widely accessible and comprehensible as possible, in keeping with the goals of the 1997 legislation. The data for each trial are standardized and presented in a clear, easy-to-read format. Users can run specific key-word searches or browse by condition, sponsor, or geographical location, making it easy to navigate the site's vast amount of information. Furthermore, knowledge of medical terminology is not presumed; the database indexes lay terms so that a search for "heart attack" will retrieve the same information as a search for "myocardial infarction." The site also contains a glossary of terms and answers to frequently asked questions about clinical trials.

* * * * *

> The site now contains records from trials in all 50 states and more than 90 countries[10] and it has logged over 75 million hits since its launch. *In April 2002,* Time *magazine named ClinicalTrials.gov as the country's best overall online health resource.* The technology and processes developed by the ClinicalTrials team have proven to be effective and promise to play an important role in the future management and dissemination of critical medical information.

Ex. 1077 (Harvard Award) at 2.

151. In my experience, the award to ClinicalTrials.gov is well deserved: the National Institutes of Health has a well-earned reputation as one of the most reliable sources of information related to clinical trials, particularly, and the medical field, generally. Thus, a POSA would have known that the ClinicalTrials.gov website, as a service of the National Library of Medicine and the National Institutes of Health, hosted information that accurately reflected the status, planning, and outcomes of the listed clinical trials.

152. That a POSA would have recognized the authoritative, accessible nature of ClinicalTrials.gov, at least because of its reliable information and readily

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[10] According to ClinicalTrials.gov, this number is now 221 countries. Ex. 1076 (ClinicalTrials.gov Background) at 2.

searchable database, is reflected by the fact that researchers regularly identified its scientific value, and cited it, and still do, as a source of publication-quality data. *See, e.g.*, Ex. 1062 (Zarin) at 2 ("The ClinicalTrials.gov trial registry was launched more than a decade ago [i.e., more than a decade before Zarin's 2011 publication date]. … The *registry now contains information on more than 100,000 clinical studies and has emerged as a key element of many public health policy initiatives* aimed at improving the clinical research enterprise." (emphasis added)); Ex. 1064 (Monami) at 2 (relying on Clinicaltrials.gov, and other sources, for a comprehensive, pre-priority date meta-analysis of human clinical trials involving GLP-1 receptor agonists, including exenatide, liraglutide, albiglutide, semaglutide, and lixisenatide); Ex. 1065 (Tasneem) at 1, 3 (reporting on an attempt to create a tool for aggregate analysis of the data on Clinicaltrials.gov and noting that the authors "chose ClinicalTrials.gov for [their] study because it is the largest database of its kind and because it covers the full range of clinical conditions, includes a broad group of trial sponsors, and has a regulatory mandate.").

153. Based on the above, a POSA therefore would have known, before the priority date of the '462 patent, that the ClinicalTrials.gov website was a searchable, comprehensive database of clinical trial information. A POSA seeking information about trials involving GLP-1 receptor agonists could and would have searched the

ClinicalTrials.gov website and would have been presented with the information found on Exhibits 1013 and 1014.

154. My experience with the ClinicalTrials.gov website before and after the priority date of the ’462 patent reflects this conclusion. First, I was listed as the principal investigator on a study identified as “Metabolic Effects of Alcohol” and listed under clinical trial registration number NCT00167115. *See generally* Ex. 1079 (NCT115). In Clinicaltrials.gov, that trial is listed as “First Posted: September 14, 2005,” and “Last Update Posted: July 10, 2012,” bracketing the priority date of the ’462 patent. Ex. 1079 (NCT115) at 1. Second, I was also listed as the principal investigator on a study identified as “Post-Gastric Bypass Hypoglycemia” and listed under clinical trial registration number NCT01933490. *See generally* Ex. 1080 (NCT490). In Clinicaltrials.gov, that trial is listed as “First Posted: September 2, 2013,” and “Last Update Posted: November 1, 2019.” *See* Ex. 1080 (NCT490) at 1. Thus, not only did I have access to ClinicalTrials.gov to search for information, but information about my own clinical trials was archived on the site, and anyone interested in the information could use the site’s search capacity to review and analyze the clinical trial information.

155. Similarly, Exhibits 1013 and 1014 are archived versions of the ClinicalTrials.gov pages for the NCT00696657 and NCT00851773 clinical trials, respectively, as retrieved and stored by the Internet Archive’s Wayback Machine

service.[11] These Exhibits reflect the information that would have been available to a POSA on the ClinicalTrials.gov website for each clinical trial as of the date the page

[11] I understand that the Patent Office's Manual of Patenting Examining Procedure discusses the Wayback Machine and considers its archived materials to be "publicly accessible at the date and time provided in the time stamp" for any retrieved materials. *See* Manual Pat. Examining Proc. § 2128.II.E ("Printed Publications" as Prior Art) ("The Wayback Machine® is a digital library maintained by the Internet Archive (a non-profit organization) for viewing information on archived digital Internet webpages. Simply, the Wayback Machine® uses software programs, known as crawlers, to surf the Internet and automatically store copies of Web objects (Web pages, images, videos, etc.), preserving these objects as they exist at the point and time of capture. These Web objects are stored as Web captures with the capture time/date in the form of a time stamp and the URL of the original website of capture. Accordingly, the Wayback Machine® provides the ability to view and browse Internet information that may no longer be available on the original website. … Prior art obtained via the Wayback Machine® sets forth a *prima facie* case that the art was publicly accessible at the date and time provided in the time stamp.") Available at: https://www.uspto.gov/web/offices/pac/mpep/s2128.html (last accessed March 11, 2023).

was archived (in this case, before the priority date of the ’462 patent), and various updates would have been available separately (as reflected by the “last updated” notations on the various captures; *see, e.g.*, Ex. 1014 (NCT773) at 7 (last updated July 15, 2010), 11 (last updated August 26, 2009)). As such, the exhibits reflect clinical trial information that a POSA could have located easily using the ClinicalTrials.gov website’s search tools, and were reviewable by and publicly available to a POSA.

156. I understand that a prior art reference is proven to be a “printed publication” upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it. I also understand that for an electronic publication, including an online database or Internet publication, to be considered a prior art printed publication, the publication must have been accessible to persons concerned with the art to which the document relates. Finally, I understand that documents obtained via the Wayback Machine are presumed to be publicly accessible at the date and time provided in the time stamp in the archived document’s web address. *See* Manual Pat. Examining Proc. § 2128.II.E (footnote 11 *supra*).

157. In view of these considerations, it is my opinion that ClinicalTrials.gov was a publicly accessible, prior art printed publication as of the priority date of the ’462 patent.

F. Other Art that Informs the POSA’s Knowledge

158. I understand that each of the references described below is prior art to the claims of the ’462 patent. Each of them would have contributed to the POSA’s knowledge of the treatment of type 2 diabetes using GLP-1 receptor agonists, generally, and semaglutide, specifically, and their formulations.

1. Drucker 2003 (Ex. 1023)

159. Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003) (“Drucker 2003”), was published in 2003.

160. Drucker 2003 disclosed that “GLP-1R agonists and DPP-IV inhibitors have shown promising results in clinical trials for the treatment of type 2 diabetes.” Ex. 1023 (Drucker 2003) at 1.

161. Drucker 2003 further disclosed that NN2211 was liraglutide, and that NN2211/liraglutide was a DPP-IV-resistant GLP-1 derivative being investigated in Phase II clinical trials:

> NN2211 (liraglutide) is a fatty acid-linked DPP-IV-resistant derivative of GLP-1 designed for subcutaneous administration that exhibits a pharmacokinetic profile compatible with once-daily injection. NN2211 reduced

> fasting and postprandial glycemia in diabetic subjects after a single 10 μg/kg subcutaneous injection at 11:00 P.M., in association with inhibition of gastric emptying and reduced levels of circulating glucagon. NN2211 has been tested in phase 2 clinical trials.

Id. at 5 (citations omitted).

162. Drucker 2003 also noted that an additional approach to prolong the duration of action of a GLP-1 derivative would be the use of albumin-bound GLP-1 molecules. *Id*.

2. Holst 2004 (Ex. 1028)

163. Holst and Deacon, *Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus*, 4 CURRENT OPINION IN PHARMACOLOGY 589 (2004) ("Holst 2004"), was published in 2004.

164. Holst 2004 disclosed that deficiencies in GLP-1 secretion and/or impaired sensitivity of β-cells to GLP-1, among other defects, exist in patients with type 2 diabetes. Ex. 1028 (Holst 2004) at 1. Holst 2004 reported that, as a result, there was "great interest in trying to develop GLP-1 as a new therapeutic agent for [type 2 diabetes mellitus]," with the benefit that "GLP-1 has many more actions than merely stimulating insulin secretion, and all of these seem to be expedient in the context of diabetes therapy." *Id*.

165. Holst 2004 identified at least the following actions of GLP-1:

a) GLP-1 potently stimulates insulin secretion in a strictly glucose-dependent manner;

b) GLP-1 stimulates all steps of insulin biosynthesis, as well as insulin gene transcription;

c) GLP-1 has trophic (growth) effects on β-cells, including stimulating β-cell proliferation and enhancing differentiation of new β-cells from progenitor cells in the pancreatic duct epithelium;

d) GLP-1 strongly inhibits glucagon secretion;

e) GLP-1 inhibits gastrointestinal secretion and motility, notably gastric emptying;

f) GLP-1 inhibits appetite and food intake; and

g) GLP-1 has cardiovascular actions, such as cardioprotective effects, via GLP-1 receptors in the heart.

Id. at 1-2.

166. Holst 2004 reported that many of these GLP-1 actions make it useful to treat diabetes, but that GLP-1's short half-life (about two minutes) limited its use as a subcutaneous injection, even though its use as an intravenous infusion could be employed. *Id.* at 2 ("GLP-1-based therapy has unusually attractive potential in diabetes treatment").

167. When used to treat patients having type 2 diabetes, GLP-1 was known to have the following beneficial effects after up to six weeks of treatment, as catalogued by Holst 2004:

a) fasting and average plasma glucose concentrations were lowered by approximately 5 mmol/L;

b) glycated haemoglobin (HbA1c) decreased by 1.2%;

c) free fatty acids were lowered significantly;

d) patients had a gradual weight loss of approximately 2 kg;

e) insulin sensitivity almost doubled;

f) insulin secretion capacity improved greatly; and

g) few side effects (no differences between saline- and GLP-1-treated patients).

Id.

168. Holst 2004 noted that, given the potential of GLP-1's use to treat type 2 diabetes, two approaches to developing therapeutically-effective compounds were taken: "development of DPP-IV-resistant analogues of GLP-1 and development of inhibitors of DPP-IV." *Id*.

169. In the category of the several described DPP-IV-resistant analogs, Holst 2004 disclosed that "NovoNordisk in Denmark developed an acylated derivative of

GLP-1 that binds non-covalently to albumin"; this was NN2211, also known as liraglutide. *Id.* at 3.

170. As disclosed by Holst 2004, liraglutide:

> consists of native GLP-1, in which a C16 acyl chain is attached via a glutamoyl spacer to Lys26 (Lys34 was substituted by Arg). The compound shows a slow release from the subcutaneous injection site and binds to albumin, which renders the molecule resistant to DPP-IV and allows at least the bound fraction to escapes [sic] renal elimination. This resulted in a half-life in healthy subjects and patients with T2DM of 10–12 h following a single subcutaneous injection and thereby adequate 24 h exposure after a single daily injection. In addition, in chronic treatment, the large post-injection concentration excursions caused by less long-lived analogues that might be associated with side effects such as nausea are likely to be avoided, as shown in studies in pigs.

Id. at 3.

171. Holst 2004 also disclosed that liraglutide "is equipotent to GLP-1 at the cloned human GLP-1 receptor," and, in clinical studies, reduced fasting and meal-related glycaemia by modifying insulin secretion, delaying gastric emptying, and suppressing post-meal glucagon secretion, all without inducing the development of anti-liraglutide antibodies, which a POSA would have known could be a concern.

Id. Holst 2004 summarized, "[t]his analogue clearly possesses favorable pharmacokinetic properties." *Id*.

3. Knudsen 2001 (Ex. 1031)

172. Knudsen et al., *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26 DRUGS OF THE FUTURE 677 (2001) ("Knudsen 2001"), is a review article published in 2001.

173. Knudsen 2001 disclosed that GLP-1 has many favorable qualities making it "an obvious drug candidate for the treatment of type 2 diabetes." Ex. 1031 (Knudsen 2001) at 1. Among these, Knudsen 2001 noted GLP-1's ability to "promot[e] glucose-dependent insulin release from the pancreatic β-cells," "lower plasma glucagon in a glucose-dependent manner, decrease the rate of gastric emptying, promote fullness/satiety and stimulate insulin biosynthesis, as well as proliferation of β-cells." *Id*.

174. Knudsen 2001 disclosed, however, that native GLP-1 suffered from a relatively short half-life in the body (e.g., 1-2 hours after subcutaneous administration), and therefore GLP-1-based drugs should use something like "a protracted formulation of the natural hormone," or "analogs or derivatives with improved pharmacokinetic properties." *Id*.

175. According to Knudsen 2001, GLP-1 "stimulates insulin release" after a meal, and "potently inhibits glucagon secretion." *Id.* at 2. As a result, liver glucose production drops, and blood glucose is lowered in patients with type 2 diabetes. *Id*. Interestingly, because GLP-1 also slows gastric emptying, insulin responses may be diminished in response to a meal. *Id*.

176. Further, "[b]ecause of the glucose-dependent nature of the insulinotropic and glucagonostatic actions of GLP-1, the glucose lowering effect of this hormone is self-limiting and, therefore, it does not cause serious hypoglycemia regardless of dose," i.e., "GLP-1 can cause blood glucose to decrease temporarily to below normal, but never leads to profound and lasting hypoglycemia." *Id*.

177. GLP-1 was also shown to "increase the rate of insulin biosynthesis" and preserve the function and cause growth of β-cells. *Id*.

178. Aside from these direct effects on blood glucose, GLP-1 was considered to have indirect effects, including "lower food intake in both rodents and humans, indirectly leading to improved glucose control via loss of body weight." *Id*.

179. Summarizing the paper's thoughts on GLP-1, generally, Knudsen 2001 stated:

> In conclusion, the mode of action of GLP-1 seems to be ideal for the treatment of type 2 diabetes, especially obese type 2 diabetes patients. GLP-1 compounds glucose-dependently stimulate insulin secretion and inhibit

> glucagon secretion, decrease gastric emptying and mediate increased fullness and/or appetite, and directly stimulate growth and rescue of pancreatic β-cells. With this important spectrum of effects of GLP-1, it is conceivable that a GLP-1-based compound could potentially be more effective than any of the current blood glucose lowering drugs available today.

Id. at 3.

180. But recalling GLP-1's relatively short half-life, Knudsen 2001 stated that a preferred GLP-1 drug would have a longer half-life with fewer peak concentrations (for example, using compounds that allow once-daily dosing rather than those that require dosing several times a day), with one avenue to this result being the creation of derivatives having long fatty acid side chains, which "could be dosed once daily and provide active plasma concentrations throughout the day." *Id*. Knudsen 2001 then described GLP-1 derivatives that could be used for once-daily administration. *Id.* at 3-5.

181. Knudsen 2001 disclosed that a preferred GLP-1 derivative was NN2211, also known as liraglutide, and disclosed its sequence. *Id.* at 4 (Fig. 1; Table 1, compound 5), 5.

182. Knudsen 2001 described NN2211 (liraglutide) as "a full agonist with equal potency to GLP-1 on the cloned human GLP-1 receptor," whose "mechanism

of protraction involves binding to albumin, metabolic stability towards DPP-IV and slow release from the injection site." *Id.* at 5.

183. In support, Knudsen 2001 noted that NN2211 had been studied extensively in pigs, where it "lowered blood glucose to near normal levels after 2-4 weeks of once-daily administration and normalized prandial glucose tolerance." *Id*. Knudsen 2001 also noted that NN2211's efficacy appeared to exceed that of exendin-4, another GLP-1 receptor agonist, and that the "differences between NN2211 and exendin-4 may be explained by the longer half-life of NN2211." *Id.* at 6.

184. Knudsen 2001 concluded:

> In summary, in a broad spectrum of animal models NN2211 has been shown to lower blood glucose and body weight, and to increase or maintain β-cell mass. All the effects are consistent with the known physiological effects of GLP-1. In humans, a study in type 2 diabetic patients has shown that a single injection of 0.010 mg/kg NN2211 lowered blood glucose from 8.1 ± 1.0 mM to 6.9 ± 1.0 mM ($p = 0.004$) (82). NN2211 is currently in phase 2 clinical trials where it's [sic] long-term efficacy will be evaluated.

Id.

4. Knudsen 2004 (Ex. 1032)

185. Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 JOURNAL OF MEDICINAL CHEMISTRY 4128 (2004) ("Knudsen 2004"), is a review article published in 2004.

186. Knudsen 2004 reported on developments related to the GLP-1 receptor agonist class of compounds and noted "the current belief is that the GLP-1 compound class may be able to control the progression of the type 2 diabetes disease not only by controlling blood glucose but also via several other effects," and appeared to have other broader effects throughout the body, such as protecting from cardiovascular complications. Ex. 1032 (Knudsen 2004) at 1; *see also id.* at 5 (noting that "GLP-1 may even exert a cardiovascular protecting effect either indirectly via lowering of blood glucose and plasma lipids or directly via specific GLP-1 receptors on the heart.").

187. Knudsen 2004 noted that administering GLP-1 is relatively risk-free because its primary action is only to "stimulate[] the natural glucose-induced insulin secretion." *Id.* at 1. Knudsen 2004 went on to note that:

> The only known pharmacological side effect of GLP-1 is nausea and vomiting when administered in high doses. These unwanted effects are mediated by inhibited gastric emptying. However, the vast majority of clinical data indicate that the nausea is transient and that efficient glucose control can be obtained without this side effect.

> Thus, from a clinical point of view, GLP-1, with its efficacious lowering of blood glucose with little risk of hypoglycemia and its potential for prevention of disease progression, seems ideal for the treatment of type 2 diabetes.

Id.

188. Knudsen 2004 described how "the efficacy of a GLP-1-like drug will be dependent on the duration of action of the compound or the formulation even though some of the long-term benefits of GLP-1 compounds, like increasing β-cell mass, may not require constantly elevated GLP-1 levels," but also noted "that long-term efficacy can be obtained without major gastrointestinal side effects." *Id.* at 1-2.

189. Regarding NN2211 (liraglutide) specifically, Knudsen 2004 disclosed that liraglutide has a half-life in humans of 11-15 hours that is effected by self-association and albumin binding; also noted was that liraglutide had completed Phase II testing at a once-daily dosing schedule. *Id.* at 2 (Table 1).

190. Knudsen 2004 also disclosed that increasing the half-life of GLP-1 receptor agonists is the drug discovery goal: "it is clear that therapeutics for the GLP-1 receptor will be peptides, and thus, the drug discovery challenge is to make a stable compound with a long half-life." *Id.* at 3.

191. In a summary of some information known about liraglutide, Knudsen 2004 disclosed several PK/PD characteristics, and stated that "for acylated derivatives of GLP-1[, like liraglutide,] the [structure-activity relationship] is well understood":

> Novo Nordisk has completed phase 2 clinical trials with liraglutide(γ-L-glutamoyl(*N*-α-hexadecanoyl))-Lys^{26},Arg^{34}-GLP-1(7-37) (NN2211) (Figure 2) as a once daily injection therapy. Several preclinical and clinical studies have been published. Liraglutide is equipotent to GLP-1 and has a half-life that is more than 10-fold larger that of exendin-4, 8 h vs 26 min after iv administration, respectively. Liraglutide is part of a series of acylated derivatives of GLP-1 that are aimed at being long-acting via two independent mechanisms, self-association and noncovalent binding to plasma albumin fatty acid binding sites, resulting in a pharmacokinetic profile with slow absorption and a long half-life. Albumin thus serves as a buffer reservoir for liraglutide. GLP-1 can be acylated at multiple sites with a hexadecanoyl fatty acid and a γ-Glu amino acid as a spacer, and the acylated GLP-1 exhibits retained potency and a long half-life after subcutaneous administration. Also, with a slightly shorter fatty acid, dodecanoyl, it is possible to attach two fatty acids and still have a potent compound with a significantly protracted profile. Spacers other than γ-Glu can be used, e.g., GABA

> or β-Ala. A potency-destroying SAR has also been generated in which acylation in the N-terminus position 8 leads to a compound about 20 times less potent than GLP-1. Acylation with two fatty acids on both naturally present lysines in positions 26 and 34 destroys potency. Last, simultaneous acylation in position 34 combined with a modification of the natural histidine in position 7 (des-aminohistidine) aimed at making the N-terminus more resistant to DPP-IV also destroys potency. Thus, for acylated derivatives of GLP-1 the SAR is well understood.

Id. (footnotes omitted).

192. Knudsen 2004's Figure 2, identified in the passage above, showed the sequence of liraglutide (top sequence):

Liraglutide: **((γ-L-Glutamoyl(N-ε-hexadecanoyl))**

His^{7}-Ala-Glu-Gly^{10}-Thr-Phe-Thr-Ser-Asp^{15}-Val-Ser-Ser-Tyr-Leu^{20}-Glu-Gly-Gln-Ala-Ala^{25}-Lys -Glu-Phe-Ile-Ala^{30}-Trp-Leu-Val-**Arg**-Gly-Arg-Gly^{37}

Exenatide (natural exendin-4):

His^{7}-Gly-Glu-Gly^{10}-Thr-Phe-Thr-Ser-Asp^{15}-Leu-Ser-Lys-Gln-Met^{20}-Glu-Glu-Glu-Ala-Val^{25}-Arg-Leu-Phe-Ile-Glu^{30}-Trp-Leu-Lys-Asn-Gly-Gly-Pro^{37}-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser

Figure 2. Structures of liraglutide and exenatide, the two first-generation products in the GLP-1 class.

Id.

193. Figure 3 from Knudsen 2004 identified the residues in GLP-1 that are essential for binding to the receptor:

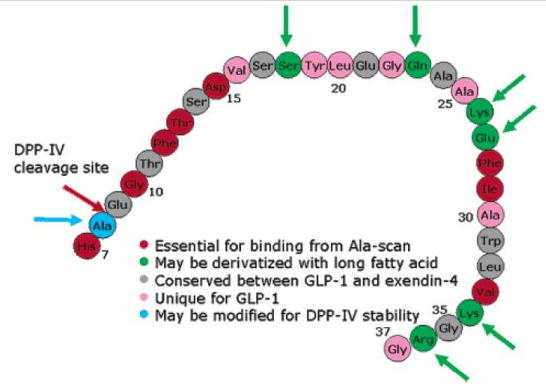

Figure 3. SAR figure of GLP-1. All sites essential for binding from Ala-scan are also conserved between GLP-1 and exendin-4. Sites that are possible to modify with fatty acids are only color-coded as such. They are all unique for GLP-1 at the same time.

Id.

194. According to Knudsen 2004 Figure 3, the amino acids essential for binding are His7, Gly10, Phe12, Thr13, Asp15, Phe28, Ile29, and Val33. *Id*.

195. Further, Knudsen 2004 identified what would make a successful GLP-1 drug product: "a convenient product with administration once daily or less." *Id.* at 4. As well, Knudsen 2004 noted that since gastrointestinal side effects are so common from peak concentrations after administering GLP-1, "[n]ausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations." *Id*.

196. Regarding treatment of diabetes, Knudsen 2004 disclosed current trial data and summarized that "data indicate that glucose control with the GLP-1 compound class may be significantly better than any of the oral drugs currently on the market for type 2 diabetes." *Id.* at 4-5. Specifically related to liraglutide, Knudsen 2004 disclosed that "[l]iraglutide has been shown to have linear dose-dependent

pharmacokinetic properties in man, with a half-life of 11-15 h and a t_{max} of 9-11 h after [subcutaneous] administration and an absolute bioavailability of 55%. Thus, the half-life should be in agreement with full efficacy following once daily administration." *Id.* at 5 (footnotes omitted).

197. Knudsen 2004 also identified other qualities of the GLP-1 drug class that suggested their ability "to delay or perhaps even prevent disease progression," such as "the potential long-term ability of GLP-1 to improve the β-cell function" and the fact that "injection of liraglutide has been shown to restore glucose sensitivity to β-cells in patients with type 2 diabetes." *Id*.

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

198. U.S. Patent No. 6,268,343 ("Knudsen patent"), titled "Derivatives of GLP-1 Analogs," issued on July 31, 2001.

199. The Knudsen patent disclosed "GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods for making an[d] using same. The GLP-1 derivatives of the present invention have a protracted profile of action." Ex. 1034 (Knudsen patent) at Abstract; *see also id.* at 1:24-27 ("The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments and/or analogues thereof which have a protracted profile of action and to methods of making and using them.").

200. The Knudsen patent disclosed that "[w]hen native peptides or analogues thereof are used in therapy it is generally found that they have a high clearance. A high clearance of a therapeutic agent is inconvenient in cases where it is desired to maintain a high blood level thereof over a prolonged period of time since repeated administrations will then be necessary," and that GLP-1 is an example of a therapeutic peptide with high clearance. *Id.* at 1:33-38, 41.

201. The Knudsen patent further disclosed that "GLP-1 is the most potent insulinotropic substance known. Unlike [glucose-dependent insulinotropic polypeptide], it is surprisingly effective in stimulating insulin secretion in NIDDM [i.e., non insulin-dependent diabetes mellitus] patients. In addition, and in contrast to the other insulinotropic hormones (perhaps with the exception of secretin) it also potently inhibits glucagon secretion. Because of these actions it has pronounced blood glucose lowering effects particularly in patients with NIDDM." *Id.* at 2:11-18.

202. The Knudsen patent disclosed that GLP-1 was "already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism," *id.* at 2:21-23, and that native GLP-1 was one of the products of a glucagon gene that could be processed by the body in a variety of ways, *id.* at 2:24-50, 4:17-35, with native GLP-1 having a plasma half-life in humans of approximately two minutes, *id.* at 2:54-55.

203. Knudsen disclosed that, before the priority date of the ’462 patent, “[t]he incretin function of GLP-1 … [had] been clearly illustrated,” with the “action of the hormone … best described as a potentiation of glucose stimulated insulin release.” *Id.* at 2:61-3:11. The Knudsen patent also noted that the beneficial, blood glucose-lowering effects are robust and self-limiting:

> if the plasma GLP-1 concentrations increase either by increased secretion or by exogenous infusion the molar ratio of insulin to glucagon in the blood that reaches the liver via the portal circulation is greatly increased, whereby hepatic glucose production decreases. As a result blood glucose concentrations decrease. Because of the glucose dependency of the insulinotropic and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore, does not cause hypoglycaemia regardless of dose. The effects are preserved in patients with diabetes mellitus, in whom infusions off slightly supraphysiological doses of GLP-1 may completely normalise blood glucose values in spite of poor metabolic control and secondary failure to sulphonylurea. The importance of the glucagonostatic effect is illustrated by the finding that GLP-1 also lowers blood glucose in type-1 diabetic patients without residual β-cell secretory capacity.

Id. at 3:25-42 (citations omitted).

204. The Knudsen patent described how "GLP-1 and analogues of GLP-1 and fragments thereof are useful i.a. in the treatment of Type 1 and Type 2 diabetes and obesity," and identified many prior art teachings regarding such derivatives and fragments. *Id.* at 4:36-5:3. The Knudsen patent noted that prior art compounds were not as useful as they could be, because of their high clearance rates; therefore, the Knudsen patent "provide[d] derivatives of GLP-1 and analogues thereof which have a protracted profile of action relative to GLP-1 (7-37)," "derivatives of GLP-1 and analogues thereof which have a lower clearance than GLP-1 (7-37)," and "a pharmaceutical composition with improved solubility and stability." *Id.* at 5:4-15.

205. To address these goals, the Knudsen patent disclosed "GLP-1 derivatives … [that] have interesting pharmacological properties, in particular they have a more protracted profile of action than the parent peptides"; further, the disclosed "GLP-1 derivatives … have insulinotropic activity, ability to decrease glucagon, ability to suppress gastric motility, ability to restore glucose competency to beta-cells, and/or ability to suppress appetite/reduce weight." *Id.* at 8:14-22.

206. Mechanistically, to achieve these goals, the Knudsen patent disclosed substituting one or both Lys residues in the GLP-1 derivatives with a "lipophilic substituent," *id.* at 12:23-25, although, "[p]referably, the GLP-1 derivatives . . . have only one Lys," *id.* at 12:27-29; *see also id.* at 16:57-65 ("To obtain a satisfactory protracted profile of action of the GLP-1 derivative, one or more lipophilic

substituents are attached to a GLP-1 moiety. The lipophilic substituents preferably comprises 4–40 carbon atoms, in particular 8–25 carbon atoms. The lipophilic substituent may be attached to an amino group of the GLP-1 moiety by means of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid residue to which it is attached."). The Knudsen patent went on to identify numerous combinations of amino acid sequences and substituents that it asserted would satisfy these goals and conditions. *See generally id.* at cols. 9-167.

207. The Knudsen patent disclosed that its GLP-1 derivatives with protracted effect could be used to treat non-insulin dependent diabetes mellitus by administering to a patient a therapeutically effective amount of the derivative, including by subcutaneous administration via a pen-like injection device. *Id.* at 169:50-170:27.

208. The Knudsen patent then claimed "[a] method of treating diabetes, comprising administering to a patient a therapeutically effective amount of a GLP-1 derivative of claim 1," *id.* at 268:49-51, and the GLP-1 derivative of claim 1 is a GLP-1 derivative with a lipophilic substituent coupled to the lysine residue at position 26, optionally with a spacer that can be an amino acid residue other than cysteine, *id.* at 265:57-267:30.

6. Lund (Ex. 1035)

209. Lund et al., *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011) ("Lund"), was published online on September 9, 2011.[12]

210. Lund's disclosures were described above. *See* Section VII.E.

7. Victoza label (Ex. 1039)

211. Victoza, whose active ingredient is liraglutide, was approved by FDA in 2010, and the first approved label describing its use issued in January 2010. Ex. 1039 (Victoza label) at 9.

212. 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.

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[12] Even if Ex. 1035 (Lund) is found not to be prior art to the claims of the '462 patent, my ultimate opinions remain the same because other prior art, described here, informed a skilled artisan's background knowledge of GLP-1 and its analogues and derivatives.

213. According to its label, Victoza was dosed and administered under the following conditions:

> • Administer once daily at any time of day, independently of meals (2).
>
> • Inject subcutaneously in the abdomen, thigh or upper arm (2).
>
> • The injection site and timing can be changed without dose adjustment (2).
>
> • Initiate at 0.6 mg per day for one week. This dose is intended to reduce gastrointestinal symptoms during initial titration, and is not effective for glycemic control. After one week, increase the dose to 1.2 mg. If the 1.2 mg dose does not result in acceptable glycemic control, the dose can be increased to 1.8 mg (2).
>
> • When initiating Victoza, consider reducing the dose of concomitantly-administered insulin secretagogues to reduce the risk of hypoglycemia (2).

Id. at 2.

214. 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.*

215. The label described Victoza (liraglutide) as being "made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on the remaining lysine residue at position 26 of the peptide precursor." *Id.* at 5.

216. As to a product description, the Victoza label stated that:

> Victoza is a clear, colorless solution. Each 1 mL of Victoza solution contains 6 mg of liraglutide. Each pre-filled pen contains a 3 mL solution of Victoza equivalent to 18 mg liraglutide (free-base, anhydrous) and 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.

217. As to Victoza's mechanism of action, the Victoza label described its effects as occurring via the GLP-1 receptor, as would be expected for a GLP-1 receptor agonist:

> Liraglutide is an acylated human Glucagon-Like Peptide-1 (GLP-1) receptor agonist with 97% amino acid sequence homology to endogenous human GLP-1(7-37). GLP-1(7-37) represents <20% of total circulating endogenous GLP-1. Like GLP-1(7-37), liraglutide activates the GLP-1 receptor, a membrane-bound cell-surface receptor coupled to adenylyl cyclase by the stimulatory G-protein, Gs, in pancreatic beta cells. Liraglutide increases intracellular cyclic AMP (cAMP) leading to insulin release in the

> presence of elevated glucose concentrations. This insulin secretion subsides as blood glucose concentrations decrease and approach euglycemia. Liraglutide also decreases glucagon secretion in a glucose-dependent manner. The mechanism of blood glucose lowering also involves a delay in gastric emptying.

Id. at 5-6.

218. The Victoza label also noted that liraglutide has an extended half-life, and therefore an extended mechanism of action, relative to native GLP-1, in the form of GLP-1(7-37):

> GLP-1(7-37) has a half-life of 1.5-2 minutes due to degradation by the ubiquitous endogenous enzymes, dipeptidyl peptidase IV (DPP-IV) and neutral endopeptidases (NEP). Unlike native GLP-1, liraglutide is stable against metabolic degradation by both peptidases and has a plasma half-life of 13 hours after subcutaneous administration. The pharmacokinetic profile of liraglutide, which makes it suitable for once daily administration, is a result of self-association that delays absorption, plasma protein binding and stability against metabolic degradation by DPP-IV and NEP.

Id. at 6.

8. WO 03/002136 (Ex. 1041)

219. International Patent Application Publication No. WO 03/002136 ("WO136") is titled "Stable Formulation of Modified GLP-1," and published on January 9, 2003. Novo Nordisk A/S is listed as the Applicant. Ex. 1041 (WO136) at 1. The named inventors on WO136 are James Flink, Silke Møller Larsen, Simon Bjerregaard Jensen, and Dorthe Kot Engelund. *Id.*

220. WO136 described pharmaceutical formulations of GLP-1 compounds, their uses, and methods of making them, with the formulations being physically and chemically stable at high concentrations, and suitable for injection, including subcutaneous injection, intramuscular, intravenous, or infusion. *Id.* at 1, 2:4-5, 4:17-30.

221. WO136 noted that (even as of 2003), "GLP-1 … is already established as an important gut hormone with regulatory function in glucose metabolism and gastrointestinal secretion and metabolism." *Id.* at 1:30-32.

222. And WO136 stated that developing such formulations was important because "[i]t is an important technical challenge to ensure prolonged stability during storage (shelf life) of many protein based drug products due to the inherent lability of macromolecules"; for example, "GLP-1 [was] known to be prone to instability due to aggregation," and, further, degradation by both chemical and physical

"pathways may ultimately lead to loss of biological activity of the protein drug." *Id.* at 3:12-20.

223. WO136 disclosed that formulating certain modified GLP-1 or analogues thereof in aqueous solution with a buffer makes the proteins "physically stable at high concentrations of the modified GLP-1 or analogues thereof, when kept in the pH range from about 7 to about 10," and "chemically stable thus rendering them shelf-stable and suitable for invasive (eg. injection, subcutaneous injection, intramuscular, intraveneous [sic] or infusion) as well as non-invasive (eg nasal or pulmonary, transdermal or transmucosal e.g. buccal) means of administration." *Id.* at 4:17-26. WO136 also disclosed that the GLP-1-related compound could be "GLP-1 (7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer," and that the formulation could include the GLP-1 compound, including liraglutide, "in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10." *Id.* at 4:32–5:14, 23:6-12, 23:29–35:29 (describing various GLP-1-related compounds and their components). WO136 has an extensive discussion of various formulation options and uses within these parameters. *See generally id.* at 5–17.

224. Among the disclosed formulation options and uses, WO136 disclosed that the GLP-1(7-37) analog could be used to reduce blood glucose levels and to treat type 2 diabetes. *See* e.g., *id.* at 14:29-30, 15:18-24 ("In a further aspect the

present invention relates to use of a GLP-1 compound for the preparation of a pharmaceutical formulation comprising an aqueous solution of the GLP-1 compound, and a buffer, wherein said GLP-1 compound is GLP-1 (7-37) or an analogue thereof wherein an amino acid residue of the parent peptide has a lipophilic substituent attached optionally via a spacer, wherein said GLP-1 compound is present in a concentration from 0.1 mg/ml to 100 mg/ml, and wherein said formulation has a pH from 7.0 to 10, for treating diabetes type II.").

225. WO136 also disclosed that determining the appropriate amount of a GLP-1 analog to use in such a formulation (i.e., an "effective amount") was well within the abilities of a doctor:

> The term "an effective amount" is the effective dose to be determined by a qualified practitioner, who may titrate dosages to achieve the desired response. Factors for consideration of dose will include potency, bioavailability, desired pharmacokinetic/pharmacodynamic profiles, condition of treatment (e.g. diabetes, obesity, weight loss, gastric ulcers), patient-related factors (e.g. weight, health, age, etc.), presence of co-administered medications (e.g. insulin), time of administration, or other factors known to a medical practitioner.

Id. at 14:17-23.

226. WO136 also disclosed that the described formulations of GLP-1(7-37) analogs could be used to treat patients, including by subcutaneous (i.e., parenteral) injection:

> The term "treatment" is defined as the management and care of a patient, e.g. a mammal, in particular a human, for the purpose of combating the disease, condition, or disorder and includes the administration of a GLP-1 compound to prevent the onset of the symptoms or complications, or alleviating the symptoms or complications, or eliminating the disease, condition, or disorder. Pharmaceutical compositions containing a GLP-1 compound according to the present invention may be administered parenterally to patients in need of such a treatment. Parenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe. Alternatively, parenteral administration can be performed by means of an infusion pump. A further option is a composition which may be a solution or suspension for the administration of the GLP-1 compound in the form of a nasal or pulmonal spray. As a still further option, the pharmaceutical compositions containing the GLP-1 compound of the invention can also be adapted to transdermal administration, e.g. from a patch, optionally a iontophoretic patch, or transmucosal, e.g. buccal [sic], administration.

Id. at 17:18-30.

227. Regarding the components of the described formulations, 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," with "glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate" preferred. *Id.* at 18:27-33.

228. Regarding components of the formulation, WO136 also disclosed that the 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 also taught that the pharmaceutical formulation could or would include one or more other ingredients such as a preservative, an isotonic agent, a chelating agent, a stabilizer, and a surfactant, the use of each of which was "well-known to the skilled person" in the art. *See id.* at 19:16–22:30.

229. WO136 disclosed that many GLP-1 compounds would be suitable for use in the formulations it described, and incorporated by reference multiple patent application publications providing examples of such 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, and WO 99/43341).

9. Additional prior art and references

230. In addition to the references discussed above and throughout this report, I utilize the knowledge and expertise of a skilled artisan. Also, in this report 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. Ground 1: WO421 Anticipated Claims 1–3

1. WO421 anticipated independent claim 1

231. Claim 1 of the ’462 patent recites “[a] method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” Ex. 1001 (’462 patent) at 35:42-44.

232. While it is my opinion that the preamble of claim 1 is not a claim limitation, even if it is a claim limitation, WO421 disclosed it, along with each element recited in the body of claim 1. As detailed below, WO421 anticipated claim

1 because the specification and claim 17 of WO421 each disclosed all the limitations of claim 1.

a. WO421's specification and claim 17 each disclosed the preamble of claim 1

233. With respect to the preamble ("method for treating type 2 diabetes"), WO421's specification disclosed "methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications)." Ex. 1011 (WO421) at 2:4-6. A POSA would have understood from this passage that a method "for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus" was disclosed, and that such method would be used with a patient in need of such treatment.

234. Further, with respect to the preamble, WO421's claim 17 disclosed "[a] GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide, *for use in a method of treating type 2 diabetes* …, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist" and a DPP-4 inhibitor. *See id.* at 65:27-31 (emphasis added). A POSA would have understood from this language in claim 17 that it disclosed a "method of treating type 2 diabetes," and that such method would be used with a patient in need of such treatment.

b. WO421's specification and claim 17 each disclosed the element "comprising administering semaglutide"

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

236. I understand from the title of WO421 that it relates to "combination therapy." *See id.* at 1; *see also id.* at 2:4-9 ("The present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic 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, to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof." (emphases added)).

237. Further, the specification of WO421 disclosed that the described combined administration includes administering semaglutide and a DPP-4 inhibitor "simultaneously, separately, sequentially or chronologically staggered," and that the described "combination therapy may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy." *Id.* at 37:2-24. A POSA would have understood the disclosures in these passages to include administering semaglutide alone at any point in time after administering a DPP-4 inhibitor, including as separate courses of treatment. *See id.* at 37:16-18 ("the administration of one element of the combination of the present invention may be prior to, concurrent to, or subsequent to the administration of the other element of the combination.").

238. Here, claim 1 of the '462 patent recites, "[a] method for treating type 2 diabetes, *comprising* administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof." Ex. 1001 ('462 patent) at 35:42-44 (emphasis added).

239. I understand from counsel that the term "comprising" is considered in this context to be a transitional phrase, or a phrase that separates the preamble of the claim ("method for treating type 2 diabetes") from the body of the claim ("administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof").

240. I further understand from counsel that the transitional phrase "comprising" is considered inclusive, or open-ended, such that it does not exclude from the scope of the claim any additional, unrecited elements or method steps.

241. Thus, in this case, I understand that the scope of the method of treatment with semaglutide recited in claim 1 may include administering semaglutide before, after, or with other compounds. Therefore, WO421's disclosure of a method of treatment with both semaglutide and a DPP-4 inhibitor, in which each compound may be administered "prior to, concurrent to, or subsequent to" the other, falls within the scope of, and anticipated, claim 1 of the '462 patent.

242. Indeed, a POSA would have known that DPP-4 inhibitors were typically dosed orally, and GLP-1 receptor agonists were dosed by subcutaneous injection, essentially requiring that the two compounds be administered alone and sequentially. *See* Ex. 1023 (Drucker 2003) at 6 (DPP-IV inhibitors are "[o]rally available," while GLP-1 receptor agonists are "[i]njectable"); Ex. 1024 (Drucker 2006) at 3, table (showing that DPP-4 inhibitors are administered orally and incretin mimetics like liraglutide and exenatide are administered subcutaneously); Ex. 1028 (Holst 2004) at 5 (DPP-4 inhibitors are administered orally, while GLP-1 analogs require parenteral administration).

243. Moreover, as detailed above, the specification of WO421 defined "combination therapy" broadly enough to include, e.g., first and second line therapy.

See Ex. 1011 (WO421) at 37:22-23. Thus, according to WO421's specification, it disclosed administering a DPP-4 inhibitor as a first line therapy, with semaglutide a follow-on second-line therapy, and vice versa.[13] *Id.* at 11:14-20.

244. Given this extremely broad definition of "combination therapy," *id.* at 36:9-15, which includes, for example, administration of semaglutide alone, the WO421 specification also disclosed the "comprising administering semaglutide" limitation in claim 1 of the '462 patent.

245. Additionally, given this teaching of WO421, along with numerous teachings in the art that semaglutide could be administered alone as a treatment for type 2 diabetes, a POSA reading WO421 would have immediately envisioned administering semaglutide alone.

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[13] A first line therapy is the initial intervention used in a method of treatment, while a second line therapy is an intervention that follows the first line. *See* Ex. 1022 (Drab) at 13; *see also* Ex. 1035 (Lund) at 8 ("Currently, the [American Diabetes Association/European Association for the Study of Diabetes] treatment algorithm suggests lifestyle and metformin therapy as the initial treatment for type 2 diabetes. As a second line-of-attack therapy, either SU or insulin is recommended as the well-validated Tier 1 approach and TZD or GLP-1R agonists as the less-validated, but acceptable, Tier 2 approach.").

246. I understand from counsel that if a POSA would immediately envision the claimed treatment in the prior art, that is also grounds for finding anticipation. Thus, for this reason too, WO421's specification provided an anticipatory disclosure of the "comprising administering semaglutide" limitation in claim 1 of the '462 patent.

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

248. Further, WO421's claim 17 disclosed the claim element "comprising administering semaglutide."

249. As noted above, claim 1 of the '462 patent recites, "[a] method for treating type 2 diabetes, *comprising* administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof." Ex. 1001 ('462 patent) at 35:42-44 (emphasis added).

250. As also noted above, I understand from counsel that the term "comprising" is considered in this context to be a transitional phrase, or a phrase that separates the preamble of the claim ("method for treating type 2 diabetes") from the body of the claim ("administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof").

251. I further understand from counsel that the transitional phrase "comprising" is considered inclusive, or open-ended, such that it does not exclude from the scope of the claim any additional, unrecited elements or method steps.

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

253. Thus, in this case, because the scope of the method of treatment with semaglutide recited in claim 1 of the '462 patent may include administering semaglutide before, after, or with other compounds, WO421 claim 17's disclosure of a method of treatment with "separate, sequential or simultaneous administration" of semaglutide and a DPP-4 inhibitor falls within the scope of, and anticipated, claim 1 of the '462 patent.

254. As noted above, I understand from counsel that if a POSA would immediately envision the claimed treatment in the prior art, that is also grounds for finding anticipation. Thus, for this reason too, WO421's claim 17 provided an anticipatory disclosure of the "comprising administering semaglutide" limitation in

claim 1 of the ’462 patent because a POSA would have immediately envisioned that element in the language of claim 17.

255. In my opinion, therefore, WO421’s claim 17 disclosed the element “comprising administering semaglutide” in claim 1 of the ’462 patent.

c. WO421’s specification and claim 17 each disclosed the element “once weekly in an amount of 1.0 mg”

256. WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. Ex. 1011 (WO421) at 36:23-36:5, 44:13; *see also id.* at 65:27-31 (claim 17, reciting administering a GLP-1 receptor agonist in a method of treating type 2 diabetes). Initially, a POSA would have understood from this passage that WO421 disclosed the use of semaglutide once weekly in a method for treating type 2 diabetes mellitus.

257. But in addition, a POSA would have understood that the disclosed range of semaglutide doses in WO421 included a discrete dose of 1.0 mg. A POSA would *not* have viewed the disclosed range of doses in WO421 (“0.1-1.6 mg”) to be an infinite range determined without regard to the practicalities of methods of administration or to the available doses of existing GLP-1 receptor agonists. Instead, a POSA would have understood, for at least two reasons, that the disclosed range in WO421 included a discrete number of steps, proceeding in increments of no less than 0.1 mg.

258. First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram. *See* Ex. 1039 (Victoza label) at 2 (showing doses of 0.6 mg, 1.2 mg, and 1.8 mg). Indeed, the dosing increments for Victoza are in increments of 0.6 mg (i.e., 0.6 mg plus 0.6 mg leads to the next dose of 1.2 mg, and adding another 0.6 mg leads to the next dosing increment of 1.8 mg).

259. Second, a POSA would have known that semaglutide was being tested in clinical trials before the priority date, including those using once weekly subcutaneous administration of semaglutide. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. A POSA would have known that, in those trials, semaglutide was tested at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg ("1.6 mg with titration"), *see* Ex. 1013 (NCT657) at 15-16, and doses of 0.1, 0.2, and 0.4 mg, 0.8 mg with titration, and 1.2 mg with titration, *see* Ex. 1014 (NCT773) at 7. It is therefore apparent that the smallest dose step size used in NCT657 or NCT773 was 0.1 mg. Moreover, in the first trial, the dosing was done in "doubling" increments. So, viewing the smallest stepwise increase as 0.1 mg is a conservative estimate of how POSAs would have looked at appropriate dosing increments.

260. Thus, a POSA would have viewed the disclosed range of doses in WO421 as including, <u>at most</u>, 16 options for dosing and would have immediately

envisioned all the options in that range at the smallest reasonable step size (i.e., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 mg).

261. I further understand that where there is a range of doses with a limited set of options, such as this, the disclosure of the range is sufficient to anticipate points in the range. Therefore, the disclosure here of the range (0.1 mg to 1.6 mg) of semaglutide administered weekly in the specification of WO421 anticipated the use of 1.0 mg semaglutide administered once weekly.

262. Separately, a POSA would have also immediately envisioned a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because, based on the prior art, POSAs would have understood that the upper end of the disclosed range was likely to be effective, even though efficacy could be found across the range. *See* Section IX.E.1.a below (as of the priority date, semaglutide had been the subject of Phase I and Phase II studies, including studies with dose ranges from 0.1 mg to 1.6 mg once weekly, and 0.1 mg to 1.2 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was near or in the range from 0.8 to 1.2 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg).

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

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

265. Thus, a POSA reading claim 17 would have understood that the claimed method required administering semaglutide. The specification of WO421 disclosed that, in the methods of WO421, "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13. For all the reasons discussed just above, WO421's disclosure of this range anticipated the 1.0 mg dose recited in claim 1 of the '426 patent.

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

d. WO421's specification and claim 17 each disclosed the element "to a subject in need thereof"

267. In my opinion, WO421 disclosed administering the described dose of semaglutide to a subject in need thereof, as recited in claim 1.

268. As discussed above, WO421's specification disclosed using a GLP-1 receptor in a method of treating type 2 diabetes. WO421 further disclosed that the method of treatment would be used with a patient in need of such treatment, including in patients who had not been treated previously. *See* Ex. 1011 (WO421) at 8:34-10:6 (patients to be treated may be drug naïve, not having been treated before, patients who failed earlier therapy, or patients who are ineligible for another therapy), 11:14-20 (disclosed method of using a GLP-1 receptor agonist involves administering the compound "to the patient (particularly human patient) in need thereof, such as e.g a patient as described" in WO421), 11:22-12:32 (same), 13:15-20 (same), 14:5-7 (same); *see also, e.g.*, *id.* at 65:27-31 (claim 17, reciting administering a GLP-1 receptor agonist in a method of treating type 2 diabetes). Therefore, the specification of WO421 disclosed the "to a subject in need thereof" claim limitation.

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

2. WO421 anticipated claim 2

270. Claim 2 of the ’462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.”

271. WO421’s specification disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. *Id.* at 36:23-37:5, 44:13.

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

273. In my opinion, therefore, the specification of WO421 disclosed the subject matter of claim 2 of the ’462 patent.

274. Claim 17 also disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because a POSA reading claim 17 would have understood that the claim 17 method requires administering semaglutide by parenteral administration.

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

276. The specification of WO421 disclosed that, in the methods of WO421, "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13.

277. In my opinion, therefore, at least WO421's claim 17 also disclosed the claim element "semaglutide is administered by parenteral administration" recited in claim 2 of the '462 patent.

278. Therefore, in my opinion, WO421 anticipated claim 2 of the '462 patent.

3. *WO421 anticipated claim 3*

279. Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”[14]

280. WO421’s specification disclosed the subject matter of claim 3 for all the same reasons described with respect to claim 1 and 2, and further because WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. Ex. 1011 (WO421) at 36:23-37:5, 44:13.

281. In my opinion, therefore, the specification of WO421 disclosed the subject matter of claim 3 of the ’462 patent.

282. Claim 17 also disclosed the subject matter of claim 3 for all the same reasons described with respect to claims 1 and 2, and further because a POSA reading claim 17 would have understood that the claim 17 method requires administering semaglutide by subcutaneous injection.

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[14] Claim 3 actually recites, “[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection.” (Emphasis added.) But neither claim 2 nor claim 1 recites “a solution.”

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

284. The specification of WO421 disclosed that, in the methods of WO421, "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13.

285. In my opinion, therefore, at least WO421's claim 17 also disclosed the claim 3 element reciting that semaglutide is administered "by subcutaneous injection."

286. Therefore, in my opinion, WO421 anticipated claim 3 of the '462 patent.

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287. It is therefore my opinion that WO421 anticipated claims 1-3 of the '462 patent.

B. Ground 2: Lovshin Anticipated Claims 1-3

288. The content of Lovshin is described in Section VIII.A above.

289. Claim 1 of the ’462 patent recites “[a] method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” Ex. 1001 (’462 patent) at 35:42-44.

290. While it is my opinion that the preamble of claim 1 is not a claim limitation, even if it is a claim limitation, Lovshin disclosed it, along with each element recited in the body of claim 1. As detailed below, Lovshin anticipated claim 1 because Lovshin disclosed all the limitations of claim 1.

1. Lovshin anticipated independent claim 1

a. Lovshin disclosed the preamble of claim 1

291. With respect to the preamble (“method for treating type 2 diabetes”), Lovshin disclosed that “incretins exert antidiabetic actions in a glucose-dependent manner,” and that NN9535 (semaglutide) is an “incretin-based therapy.” Ex. 1012 (Lovshin) at 2, “Key points.” A POSA would have understood from this passage (i.e., from the language “exert antidiabetic actions”) that Lovshin disclosed a “method for treating type 2 diabetes,” as recited in claim 1, and that such a method would be used with a patient in need of such treatment.

292. This conclusion is reinforced by Lovshin’s disclosure that NN9535 (semaglutide), like native GLP-1, is a GLP-1 receptor agonist, *id.* at 2, and that “[c]ontinuous, subcutaneous administration of native GLP-1 to patients with type 2

diabetes mellitus (T2DM) lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss," *id.* at 1.

b. Lovshin disclosed the element "comprising administering semaglutide"

293. In my opinion, Lovshin also disclosed the claim element "comprising administering semaglutide." With respect to this claim element, Lovshin disclosed that semaglutide was "under active clinical investigation in phase I–II studies," *id.* at 5, and a POSA would have known that phase I and II clinical studies involve administering treatments to patients.

294. In further support, Lovshin disclosed that NN9535 (semaglutide) is a GLP-1 receptor agonist (like liraglutide and exenatide), *id.* at 2 (Table 1), and that "[c]ontinuous, subcutaneous administration of native GLP-1 to patients with type 2 diabetes mellitus (T2DM) lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss," *id.* at 1. Lovshin also disclosed that liraglutide was administered once daily to patients with type 2 diabetes and was well tolerated and effectively reduced HbA_{1c} levels without hypoglycemia. *Id.* at 3.

295. Further, Lovshin disclosed that "[a] 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients

treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight." *Id.*

296. In addition, Lovshin disclosed that exenatide, the "first GLP-1 [receptor] agonist to be approved for human clinical use," was used to treat patients with type 2 diabetes. *Id.* at 2.

297. A POSA would have understood from these descriptions that semaglutide, like liraglutide, exenatide, and other GLP-1 receptor agonists, was administered to patients.

c. Lovshin disclosed the element "once weekly in an amount of 1.0 mg"

298. Lovshin disclosed that the dose of NN9535 (semaglutide) to be administered to a patient is "0.1–1.6 mg once weekly," given by "subcutaneous injection" to treat type 2 diabetes. *Id.* at 2. A POSA would have understood from this passage that Lovshin disclosed the use of semaglutide once weekly in a method for treating type 2 diabetes mellitus.

299. A POSA also would have understood that the disclosed range of semaglutide doses in Lovshin included a discrete dose of 1.0 mg. A POSA would *not* have viewed the disclosed range of doses in Lovshin ("0.1-1.6 mg") to be an infinite range determined without regard to the practicalities of methods of administration or to the available doses of existing GLP-1 receptor agonists. Instead,

a POSA would have understood, for at least two reasons, that Lovshin's disclosed range included a discrete steps proceeding in increments of no less than 0.1 mg.

300. First, a POSA would have known that, earlier than the priority date, liraglutide, a highly similar GLP-1 receptor agonist, had been approved as Victoza, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram. *See* Ex. 1039 (Victoza label) at 2 (showing doses of 0.6 mg, 1.2 mg, and 1.8 mg). Indeed, the dosing increments for Victoza are in increments of 0.6 mg (i.e., 0.6 mg plus 0.6 mg leads to the next dose of 1.2 mg, and adding another 0.6 mg leads to the next dosing increment of 1.8 mg).

301. Second, a POSA would have known at least from Lovshin that the 0.1–1.6 mg dose range was, like other once weekly GLP-1 therapies, "being investigated" in Phase I/II studies. Ex. 1012 (Lovshin) at 2 (Table 1), 5. As such, a POSA would have known that there was an expectation that the effective clinical dose of semaglutide would reside within this disclosed limited range.

302. This is further supported and confirmed by details from the known prior art clinical trials testing once weekly subcutaneous administration of semaglutide. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. A POSA would have known that, in those trials, semaglutide was tested at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg ("1.6 mg with titration"), *see* Ex. 1013 (NCT657) at 15-16, and doses of 0.1, 0.2, and 0.4 mg, 0.8 mg with titration, and 1.2 mg with

titration, *see* Ex. 1014 (NCT773) at 7. It is therefore apparent that the smallest dose step size used in NCT657 or NCT773 was 0.1 mg. Moreover, in the first trial, the dosing was done in "doubling" increments (and in the second trial, doubling applied to the first three steps). So, viewing the smallest stepwise increase as 0.1 mg is a conservative estimate of how a POSA would have looked at appropriate dosing increments.

303. Thus, a POSA would have viewed the disclosed range of doses in Lovshin as including, at most, 16 options for dosing and would have immediately envisioned all the options in that range at the smallest reasonable step size (i.e., 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, and 1.6 mg).

304. I further understand that where, as here, there is a range of doses with a limited set of options, the disclosure of the range is sufficient to anticipate points in the range. Therefore, Lovshin's disclosure of the 0.1 mg to 1.6 mg range of doses of semaglutide administered weekly anticipated the use of 1.0 mg semaglutide administered once weekly.

305. Separately, a POSA would have also immediately envisioned a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because, based on the prior art, a POSA would have understood that the upper end of the disclosed range was likely to be effective, even though efficacy could be found across the range. *See* Section IX.E.1.a below (as of the

priority date, semaglutide had been the subject of Phase I and Phase II studies, including studies with dose ranges from 0.1 mg to 1.6 mg once weekly, and 0.1 mg to 1.2 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was near or in the range from 0.8 to 1.2 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg).

306. In my opinion, therefore, Lovshin disclosed the claim element "once weekly in an amount of 1.0 mg" recited in claim 1 of the '462 patent.

d. Lovshin disclosed the element "to a subject in need thereof"

307. As discussed above, Lovshin disclosed that incretins/GLP-1 receptor agonists like semaglutide are used in a method of treating type 2 diabetes. Lovshin further disclosed that exenatide, "first GLP-1 [receptor] agonist to be approved for human clinical use," as a treatment in patients with type 2 diabetes. Ex. 1012 (Lovshin) at 2. Lovshin also disclosed that liraglutide was administered once daily to patients with type 2 diabetes and was well tolerated and effectively reduced HbA_{1c} levels without hypoglycemia. *Id.* at 3. Further, Lovshin disclosed that "[a] 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight."

Id. A POSA would have known that a person with type 2 diabetes was in need of treatment. Therefore, Lovshin disclosed the "to a subject in need thereof" claim limitation.

* * * * *

308. In my opinion, therefore, Lovshin anticipated claim 1 of the '462 patent.

2. Lovshin anticipated claim 2

309. Claim 2 of the '462 patent depends from claim 1 and recites the additional limitation that "semaglutide is administered by parenteral administration."

310. Lovshin disclosed that NN9535 (semaglutide) is administered by "subcutaneous injection." Ex. 1012 (Lovshin) at 2 (Table 1).

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

312. In my opinion, therefore, Lovshin anticipated claim 2 of the ’462 patent.

3. Lovshin anticipated claim 3

313. Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”[15]

314. Lovshin disclosed that NN9535 (semaglutide) is administered by “subcutaneous injection.” Ex. 1012 (Lovshin) at 2 (Table 1).

315. In my opinion, therefore, Lovshin anticipated claim 3 of the ’462 patent.

* * * * *

316. It is therefore my opinion that Lovshin anticipated claims 1-3 of the ’462 patent.

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

C. Ground 3: Claims 1–10 of the ’462 patent would have been obvious over WO421 alone or in view of the ’424 publication

317. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over WO421.

1. Claim 1 of the ’462 patent would have been obvious over WO421 alone

318. Claim 1 of the ’462 patent recites “[a] method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.” It is my opinion that claim 1 of the ’462 patent would have been obvious over WO421 alone.

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

319. The disclosures of WO421 are described above. *See* Sections VIII.D and IX.A.

320. WO421 disclosed “methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” 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).

321. Thus, WO421 disclosed the elements of claim 1 reciting "[a] method for treating type 2 diabetes, comprising administering semaglutide … to a subject in need thereof."

322. To the extent that WO421 is deemed not to have expressly disclosed a 1.0 mg dose of semaglutide as a treatment, as I opined above, that dose would have been obvious to a POSA in view of the prior art.

323. To explain, it is my opinion that a POSA would have been motivated to optimize the dose of semaglutide used once weekly to treat diabetes, a routine process, and it would have been obvious to a POSA to reach a dose of 1.0 mg. A POSA would have known from WO421 that the optimized dose to be used in a once weekly treatment with semaglutide would fall in the range of 0.1-1.6 mg. Ex. 1011 (WO421) at 36:23-37:5, 44:13. In particular, as detailed above, patients desired fewer injections, as compared to the prior art liraglutide and exenatide treatments, requiring daily, and twice daily injections, respectively. *See* Ex. 1040 (Vilsbøll) at 4, Table 1. A POSA would have known from the prior art that semaglutide was an option that would be provided as a once weekly injection, a significant improvement in the eyes of patients, especially those experiencing needle phobia, and an important improvement to a POSA. *See, e.g.*, Ex. 1029 (Jimenez-Solem) at 5 ("Clinical data suggests that a more stable pharmacokinetic profile (ie, a longer $t_{1/2}$) leads to higher efficacy, and lower frequencies of nausea and vomiting. Furthermore, the benefits

to patient convenience and compliance are obvious."); Ex. 1015 (WO537) at 2:26-33 ("Many diabetes patients particularly in the type 2 diabetes segment are subject to so-called 'needle-phobia', i.e. a substantial fear of injecting themselves. In the type 2 diabetes segment most patients are treated with oral hypoglycaemic agents, and since GLP-1 compounds are expected to be the first injectable product these patients will be administered, the fear of injections may become a serious obstacle for the widespread use of the clinically very promising GLP-1 compounds. Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile."). Given that semaglutide was already in the prior art, semaglutide was an obvious choice for optimization. Moreover, as detailed below, a significant amount of information was already in the prior art directing a POSA to the right dose.

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

325. As detailed previously (*see* Section IX.A.1.c above), the disclosure of the range from 0.1-1.6 mg was ultimately the disclosure of, at most, 16 possible dosing choices. However, even within the range of 16 possible doses, a POSA would have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of WO421's disclosed range, as described in more detail below. *See* Section IX.E.1. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), which shares an amino acid backbone with semaglutide, was approved in January 2010 in doses of 0.6, 1.2, and 1.8 mg. *See* Ex. 1039 (Victoza label). A POSA would also have known that Victoza's 1.2 mg dose was the targeted dose for long-term therapy, with the 1.8 mg dose used only "[i]f the 1.2 mg dose does not result in acceptable glycemic control." Victoza label at 2. And, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg ("1.6 mg with titration"), *see* Ex. 1013 (NCT657) at 15-16, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* Ex. 1014 (NCT773) at 7.

326. Further, from one or more of these disclosures (i.e., from WO421, NCT657, and/or NCT773), a POSA would have expected that by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to

use in that method, the doses disclosed in the prior art would be expected to function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work to treat type 2 diabetes.

327. Additionally, a POSA would have been motivated to try the 1.0 mg dose in the dose range disclosed by WO421. A POSA would have known from WO421 that the range of potential doses of semaglutide was 0.1-1.6 mg. Ex. 1011 (WO421) at 36:23-37:5, 44:13. And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options for dosing, as described above in detail. *See* Section IX.A.1.

328. Thus, a POSA would have been motivated to optimize the dose within the known range of 0.1 mg to 1.6 mg of semaglutide disclosed in WO421, and separately, would have been specifically motivated to try a 1.0 mg dose of semaglutide, once weekly.

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

329. A POSA would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide. A POSA would have known from the prior art that liraglutide and semaglutide shared the same amino acid backbone (i.e., the portion of the molecule that renders it effective to

bind the GLP receptor), and therefore would have reasonably expected them to behave similarly as GLP-1 receptor agonists. As further support, a POSA would have known that there were several other GLP-1-related compounds being studied, each of which was known to be effective to reduce one or more of HbA_{1c} levels, body weight, and blood glucose concentrations, while avoiding the complication of hypoglycemia, in both human and preclinical trials. *See* Ex. 1012 (Lovshin) at 2-5 (identifying, in addition to liraglutide: exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC1134, LY2199265, and LY2428757, several of which were once weekly formulations); *see also* Ex. 1035 (Lund) at 4, Table 1 (identifying, in addition to liraglutide: exenatide, exenatide once weekly, lixisenatide, CJC-1134-PC, albiglutide, and dulaglutide, several of which were once weekly formulations, two of which were launched, and four of which were in Phase III trials or expected shortly to be launched). A POSA would have reasonably expected semaglutide to behave in a generally consistent way as a GLP-1 receptor agonist, given the similarity in structure and pharmacology among the several compounds. *See* Ex. 1032 (Knudsen 2004) at 3, Fig. 3 (showing conserved important GLP-1 residues); *id.* Figs. 1 and 2 (GLP-1 and liraglutide sequences); Ex. 1001 ('462 patent) at 9:43-44 (citing Ex. 1015 (WO537) at 48:4-22 (Example 4) for semaglutide sequence) (Section IX.D.1.b below, showing conservation in liraglutide and semaglutide of residues known to be essential for binding); *see also* ¶¶ 77-78 above, (showing

nearly identical amino acid sequences for liraglutide and semaglutide); Ex. 1035 (Lund) at 4, Table 2 (showing sequence homology between GLP-1 and GLP-1 receptor agonists already on the market or in late clinical development).

330. Related, as described above, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* Ex. 1013 (NCT657) at 15-16, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* Ex. 1014 (NCT773) at 7. While the results of those clinical trials were not yet available as of the priority date, the fact that they were being tested in human clinical trials was telling. A POSA would have known that for human clinical trials to be performed, a significant body of data related to the drug at issue would have already been collected. *See generally, e.g.*, Ex. 1033 (Knudsen 2010) (describing work with numerous animal models during the development of liraglutide). Moreover, a POSA would have understood that under basic clinical trial design principles, the upper end of the chosen doses would be expected to function as intended as they reached the plateau of the drug's dose-response curve, and the bottom doses were intended or expected to be suboptimal, even if some treatment effect may be apparent across the whole (or nearly whole) dose range. *See, e.g.*, Ex. 1038 (Seino) at 4 (dose-response curve for HbA1c response

versus liraglutide dose, showing suboptimal effects for the lower doses). A POSA reading WO421 would bring this knowledge with them.

331. A POSA therefore would have optimized the known weekly dosing range for semaglutide, 0.1 mg to 1.6 mg. And separately and relatedly, would have had a reasonable expectation of success with a 1.0 mg weekly dose of semaglutide. Thus, claim 1 of the ’462 patent would have been obvious to a POSA in view of WO421.

2. Claims 2 and 3 of the ’462 patent would have been obvious over WO421 alone

332. Claim 2 of the ’462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.”

333. WO421’s specification disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. Ex. 1011 (WO421) at 36:23-37:5, 44:13.

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

POSA would have understood that the "subcutaneous injection" disclosed in WO421 is a type of parenteral administration.

335. In my opinion, therefore, the specification of WO421 disclosed the subject matter of claim 2 of the '462 patent.

336. Claim 17 also disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because a POSA reading claim 17 would have understood that the claim 17 method requires administering semaglutide by parenteral administration.

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

338. The specification of WO421 disclosed that, in the methods of WO421, "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13.

339. In my opinion, therefore, at least WO421's claim 17 also disclosed the claim element "semaglutide is administered by parenteral administration" recited in claim 2 of the '462 patent.

340. Therefore, in my opinion, claim 2 would have been obvious over WO421.

341. Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”[16]

342. WO421’s specification disclosed the subject matter of claim 3 for all the same reasons described with respect to claim 1 and 2, and further because WO421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. Ex. 1011 (WO421) at 36:23-37:5, 44:13.

343. In my opinion, therefore, the specification of WO421 disclosed the subject matter of claim 3 of the ’462 patent.

344. Claim 17 also disclosed the subject matter of claim 3 for all the same reasons described with respect to claims 1 and 2, and further because a POSA

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

reading claim 17 would have understood that the claim 17 method requires administering semaglutide by subcutaneous injection.

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

346. The specification of WO421 disclosed that, in the methods of WO421, "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13.

347. In my opinion, therefore, at least WO421's claim 17 also disclosed the claim 3 element reciting that semaglutide is administered "by subcutaneous injection."

348. Therefore, in my opinion, claim 3 would have been obvious over WO421.

* * * * *

349. It is therefore my opinion that claims 1-3 of the '462 patent would have been obvious over WO421.

3. Claims 4–10 of the ’462 patent would have been obvious over WO421 in view of the ’424 publication

350. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over WO421, as described above. My opinions are limited to the treatment of diabetes with subcutaneous administration of a once weekly 1.0 mg dose of semaglutide, as recited and claimed in claims 1–3 of the ’462 patent. However, I understand it is Dr. Dalby’s opinion that the ’424 publication disclosed all formulation-related elements of claims 4–10 of the ’462 patent.

351. It is therefore my opinion that claims 4–10 of the ’462 patent would have been obvious over WO421 in view of the ’424 publication for the reasons addressed in Section IX.C.1 and by Dr. Dalby.

* * * * *

352. It is therefore my opinion that claims 1-10 of the ’462 patent would have been obvious over WO421 alone or in view of the ’424 publication.

D. Ground 4: Claims 1–10 of the ’462 patent would have been obvious over WO537 in view of Lovshin

353. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over WO537 in view of Lovshin.

1. Claim 1 of the ’462 patent would have been obvious over WO537 in view of Lovshin

354. Claim 1 of the ’462 patent recites “[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg

to a subject in need thereof." It is my opinion that claim 1 of the '462 patent would have been obvious over WO537 in view of Lovshin.

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

355. The disclosures of WO537 are described above. *See* Section VIII.C above.

356. WO537[17] 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 48:4-22, and a patient with type 2 diabetes in need of treatment with a GLP-1 peptide, which improves glycemic control, *id.* at 23:24-26.

357. WO537 also disclosed that the compounds it described could be used to prepare a medicament for delaying, treating, or preventing disease progression for type 2 diabetes. *Id.* at 39:3-4. 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: "One aspect of this invention is to prepare GLP-1

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

analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration." *Id.* at 60:24-25.

358. WO537 also described how to screen once weekly GLP-1 analogs for activity in a mouse model:

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

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

359. Thus, WO537 disclosed the elements of claim 1 reciting "[a] method for treating type 2 diabetes, comprising administering semaglutide once weekly … to a subject in need thereof."

360. Lovshin 2009 disclosed, further, that NN9535 (i.e., semaglutide, as a POSA would have been known)[18] was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Ex. 1012 (Lovshin) at 2, Table 1. It would have been obvious to a POSA to optimize the dose of semaglutide to a dose of 1.0 mg and/or

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[18] *See also* Ex. 1035 (Lund) at 4; Ex. 1060 (WO193) at 35:18; Ex. 1057 (WO328) at 2:16-17.

the 1.0 mg dose would have been obvious to try in that disclosed dose range, and the POSA would have been motivated to do so by a desire to select the optimal treatment dose, targeting the best balance between treatment benefit and adverse events.

361. To explain, it is my opinion that a POSA would have been motivated to optimize the dose of semaglutide used once weekly to treat diabetes, and it would have been obvious to a POSA to reach a dose of 1.0 mg. A POSA would have known from Lovshin that the optimized dose to be used in a once weekly treatment with semaglutide would fall in the range of 0.1-1.6 mg. Ex. 1012 (Lovshin) at 2, Table 1 ("0.1-1.6 mg once weekly"). In particular, patients desired fewer injections, as compared to the prior art liraglutide and exenatide treatments, requiring daily, and twice daily injections, respectively. *See* Ex. 1040 (Vilsbøll) at 4, Table 1. A POSA would have known from the prior art that semaglutide was an option that would be provided as a once weekly injection, a significant improvement in the eyes of patients, especially those experiencing needle phobia, and an important improvement to a POSA. *See, e.g.*, Ex. 1029 (Jimenez-Solem) at 5 ("Clinical data suggests that a more stable pharmacokinetic profile (ie, a longer $t_{1/2}$) leads to higher efficacy, and lower frequencies of nausea and vomiting. Furthermore, the benefits to patient convenience and compliance are obvious."); Ex. 1032 (Knudsen 2004) at 4 ("Nausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations."). Given that semaglutide was

already in the prior art, semaglutide was an obvious choice for optimization. And moreover, as detailed below, a significant amount of information was already in the prior art directing POSAs to the right dose.

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

363. As detailed previously (*see* Section IX.A.1.c above), the disclosure of the range from 0.1 to 1.6 mg was ultimately the disclosure of, at most, 16 possible choices. However, even within the range of 16 possible doses, a POSA would have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of Lovshin's disclosed range, as described in more detail below. *See* Section IX.E.1. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), which shares an amino acid backbone with semaglutide, was approved in January 2010 in doses of 0.6, 1.2, and 1.8 mg. *See* Ex. 1039 (Victoza label). A POSA would also have known that Victoza's 1.2 mg dose was the targeted dose for long-term therapy, with the 1.8 mg dose used only "[i]f the 1.2 mg dose does not result in

acceptable glycemic control." Victoza label at 2. And, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* Ex. 1013 (NCT657) at 15-16, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* Ex. 1014 (NCT773) at 7.

364. Further, from one or more of these disclosures (i.e., from WO421, NCT657, and/or NCT773), a POSA would have expected that by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to use in that method, the doses disclosed in the prior art would be expected to function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work to treat type 2 diabetes.

365. In addition, a POSA would have been motivated to try the 1.0 mg dose in the dose range disclosed by Lovshin. A POSA would have known from Lovshin that the range of potential doses of semaglutide was 0.1-1.6 mg. Ex. 1012 (Lovshin) at 2, Table 1 ("0.1-1.6 mg once weekly"). And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options for dosing, as described above in detail. *See* Section IX.A.1.

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

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

367. A POSA would have had a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide. A POSA would have known from the prior art that liraglutide and semaglutide shared the same amino acid backbone (i.e., the portion of the molecule that renders it effective to bind the GLP receptor), and therefore would have reasonably expected them to behave in similar fashion as GLP-1 receptor agonists. A POSA also would have known that liraglutide and semaglutide shared amino acids known from earlier work, Ex. 1032 (Knudsen 2004) at 3, Fig. 3, to be essential for binding:

Knudsen 2004 Fig. 3 essential residue	**Present in liraglutide?**	**Present in semaglutide?**
His7	**Yes**	**Yes**
Gly10	**Yes**	**Yes**
Phe12	**Yes**	**Yes**
Thr13	**Yes**	**Yes**
Asp15	**Yes**	**Yes**
Phe28	**Yes**	**Yes**
Ile29	**Yes**	**Yes**
Val33	**Yes**	**Yes**

See Ex. 1032 (Knudsen 2004) at 3, Fig. 3; *Id.*, Fig. 2 (liraglutide sequence); Ex. 1001 ('462 patent) at 9:43-44 (citing Ex. 1015 (WO537) at 48:4-22 (Example 4) for semaglutide sequence).

368. As further support, a POSA would have known that there were several other GLP-1-related compounds being studied, each of which was known to be effective to reduce blood glucose, HbA_{1c} levels, and body weight, while avoiding the complication of hypoglycemia, in both human and preclinical trials. *See* Ex. 1012 (Lovshin) at 2-5 (identifying, in addition to liraglutide, exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC-1134-PC, LY2189265, and LY2428757, several of which were once weekly formulations); *see also* Ex. 1035 (Lund) at 4, Table 1 (identifying, in addition to liraglutide: exenatide, exenatide once weekly, lixisenatide, CJC-1134-PC, albiglutide, and dulaglutide, several of which were once weekly formulations, two of which were launched, and four of which were in Phase III trials or expected shortly to be launched). A POSA would have reasonably expected semaglutide to provide the same benefits, given that the several compounds all belonged to the same class of GLP-1 receptor agonists. Ex. 1012 (Lovshin) at 2-5; *see also* Ex. 1032 (Knudsen 2004) at 3, Figs. 1 and 2 (GLP-1 and liraglutide sequences); Ex. 1001 ('462 patent) at 9:43-44 (citing Ex. 1015 (WO537) at 48:4-22 (semaglutide sequence)); *see also* Ex. 1035 (Lund) at 4, Table 2 (showing

sequence homology between GLP-1 and GLP-1 receptor agonists already on the market or in late clinical development).

369. Related, as described above, a POSA would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (1.6 mg with titration), *see* Ex. 1013 (NCT657) at 15-16, and once weekly subcutaneous administration at doses of 0.1, 0.2, and 0.4 mg, doses leading up to 0.8 mg, and doses leading up to 1.2 mg, *see* Ex. 1014 (NCT773) at 7. While the results of those clinical trials were not yet available as of the priority date, the fact that they were being tested in human clinical trials was telling. A POSA would have known that for human clinical trials to be performed, a significant body of data related to the drug at issue would have already been collected. *See generally, e.g.*, Ex. 1033 (Knudsen 2010) (describing work with animal models during the development of liraglutide). Moreover, a POSA would have understood that under basic clinical trial design principles, the upper end of the chosen doses would be expected to function as intended, and the bottom doses were intended or expected to be suboptimal, even if they could still have some amount of treatment effect. *See, e.g.*, Ex. 1038 (Seino) at 4 (dose-response curve for HbA1c response versus liraglutide dose, showing greater treatment effect with the larger doses).

370. A POSA therefore would have optimized the known weekly dosing range for semaglutide, 0.1 mg to 1.6 mg. And separately and relatedly, a POSA would have had a reasonable expectation of success with a 1.0 mg weekly dose of semaglutide. Thus, claim 1 of the ’462 patent would have been obvious to a POSA over WO537 in view of Lovshin.

2. Claims 2 and 3 of the ’462 patent would have been obvious over WO537 in view of Lovshin

371. Claim 2 of the ’462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.”

372. WO537 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.” Ex. 1015 (WO537) at 35:15-16; *see also id.* at 35:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

373. Thus, in addition to rendering obvious the subject matter of claim 1, in conjunction with Lovshin, it is my opinion that WO537 further disclosed claim 2’s requirement that “semaglutide is administered by parenteral administration.”

374. Therefore, in my opinion, claim 2 would have been obvious over WO537 in view of Lovshin.

375. Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”[19]

376. WO537 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,” and a POSA would have understood that the injection was of a solution. Ex. 1015 (WO537) at 35:15-16; *see also id.* at 35:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

377. Thus, in addition to rendering obvious the subject matter of claims 1 and 2, in conjunction with Lovshin, it is my opinion that WO537 further disclosed claim 3’s requirement that the parenteral administration occurs “by subcutaneous injection.”

378. Therefore, in my opinion, claim 3 would have been obvious over WO537 in view of Lovshin.

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

* * * * *

379. It is therefore my opinion that claims 1-3 of the ’462 patent would have been obvious over WO537 in view of Lovshin.

3. Claims 4–10 of the ’462 patent would have been obvious over WO537 in view of Lovshin

380. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over WO537 in view of Lovshin, as described above. My opinions are limited to the treatment of diabetes with the once weekly 1.0 mg dose of semaglutide, as recited and claimed in claims 1–3 of the ’462 patent. However, I understand it is Dr. Dalby’s opinion that WO537 disclosed all formulation-related elements of claims 4–10 of the ’462 patent.

381. It is therefore my opinion that claims 4–10 of the ’462 patent would have been obvious over WO537 in view of Lovshin for the reasons addressed in Section IX.D.1 above and by Dr. Dalby.

* * * * *

382. It is therefore my opinion that claims 1-10 of the ’462 patent would have been obvious over WO537 in view of Lovshin.

E. Ground 5: Claims 1–10 of the ’462 patent would have been obvious over NCT657 in view of NCT773 and further in view of the ’424 publication

383. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over NCT657 in view of NCT773.

1. Claim 1 of the '462 patent would have been obvious over NCT657 in view of NCT773

384. Claim 1 of the '462 patent recites "[a]method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof." It is my opinion that claim 1 of the '462 patent would have been obvious over NCT657 and NCT773.

385. NCT657 disclosed a Phase 2 interventional trial in which participants with type 2 diabetes were treated "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)." Ex. 1013 (NCT657) at 15. In one of the NCT657 experimental arms, semaglutide was used as a treatment for diabetes with "0.8 mg with titration, once weekly, [subcutaneous] injection." *Id.* In another, semaglutide was used as a treatment for diabetes with "1.6 mg with titration, once weekly, [subcutaneous] injection." *Id.* at 16. The trial included six different semaglutide dosages, including 0.8 and 1.6 mg:

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

See id. at 15-16.

386. NCT657 reported that the clinical trial started in June 2008 and was completed in February 2009. *Id.* at 15.

387. Thus, NCT657 disclosed the elements of claim 1 reciting "[a] method for treating type 2 diabetes, comprising administering semaglutide … to a subject in need thereof."

388. NCT657 further disclosed that semaglutide was administered once weekly by subcutaneous injection, i.e., "(0.1 mg QW – 1.6 mg QW[)]" to treat type 2 diabetes. *Id.*

389. Thus, NCT657 expressly disclosed claim 1's requirement for dosing patients once weekly with semaglutide, claim 2's requirement that "semaglutide is administered by parenteral administration," and claim 3's requirement that the parenteral administration be "by subcutaneous injection."

390. For its part, NCT773 disclosed a Phase 1 interventional trial in which participants were treated with semaglutide (0.1 mg once weekly – 1.2 mg once weekly), in five treatment arms, or placebo. Ex. 1014 (NCT773) at 7-8. A POSA would have known from NCT657, and a variety of other prior art cited here, that semaglutide could be used to treat type 2 diabetes.

391. In one of the NCT773 experimental arms, semaglutide was administered as "0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks, [subcutaneous] injection," and in another as "0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.2 mg once weekly for 6 weeks, [subcutaneous] injection." *Id.* at 7. The trial included five different semaglutide dosing regimens, including 0.8 and 1.2 mg final dose amounts:

▼ Arms and Interventions

Arms	Assigned Interventions
Experimental: A	Drug: NN9535 0.1 mg once weekly, s.c. injection
Experimental: B	Drug: NN9535 0.2 mg once weekly, s.c. injection
Experimental: C	Drug: NN9535 0.4 mg once weekly, s.c. injection
Experimental: D	Drug: NN9535 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks, s.c. injection
Experimental: E	Drug: NN9535 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.2 mg once weekly for 6 weeks, s.c. injection

Ex. 1014 (NCT773) at 7.

392. NCT773 reported that the clinical trial started in February 2009 and was completed in October 2009. *Id.*

393. Thus, NCT773 disclosed the elements of claim 1 reciting "[a] method for treating type 2 diabetes, comprising administering semaglutide … to a subject."

394. NCT773 further disclosed that semaglutide was administered once weekly by subcutaneous injection, e.g., "0.1 mg once weekly" and "0.4 mg once weekly," *Id.* at 7, and would have known that semaglutide could be used to treat type 2 diabetes.

395. Thus, NCT773 expressly disclosed claim 1's requirement for dosing patients once weekly with semaglutide, claim 2's requirement that "semaglutide is administered by parenteral administration," and claim 3's requirement that the parenteral administration be "by subcutaneous injection."

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

396. In my opinion, a POSA would have been motivated to combine the teachings of NCT657 and NCT773 and would have arrived at a semaglutide dosing regimen for type 2 diabetes of 1.0 mg once weekly.

397. A POSA would have known that a general goal of a method of treatment is to provide a distinct treatment benefit to a patient with an acceptable level of adverse events. In this case, a POSA would have received significant guidance from the prior art to reach such a method of treatment using semaglutide, and that a dose of 1.0 mg once weekly would have satisfied the treatment goals.

398. First, a POSA would have known generally from the prior art, in addition to the teachings of NCT657 and NCT773, that semaglutide was being investigated in Phase I and Phase II trials to treat type 2 diabetes using a once weekly dose, and a dose in the range of 0.1–1.6 mg once weekly was the target. *See* Ex. 1012 (Lovshin) at 2 (Table 1), 5; *see also* Ex. 1035 (Lund) at 7-8 ("Semaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly[subcutaneous] injections, based on the GLP-1 backbone… So far, 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)."), 3 (Fig. 1) (semaglutide is a once weekly GLP-1-based treatment), 4 (Table 1) (semaglutide is a once weekly formulation in Phase II development); Ex. 1061 ('321 publication) at [0010] ("WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S."); Ex. 1040 (Vilsbøll) at 4 (semaglutide is a "GLP-1 receptor agonist[] currently on the market or in clinical development," in Phase II trials for once weekly dosing); Ex. 1011 (WO421) at 44:31 ("Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).").

399. Second, based on these disclosures, and what a POSA would have known about clinical trial planning and execution, a POSA would have known that Novo Nordisk conducted the NCT657 and NCT773 phase II and I studies as dose-ranging exercises, in which the trials tested specific, selected doses to yield a dose-response curve. This curve would, in turn, guide the selection of an optimal dose, which would be an effective dose that provided an acceptable balance of clinical benefit and adverse events; a POSA would have optimized the dose to 1.0 mg once weekly using the data points on this curve as guidance. *See* Ex. 1047 (Tamimi) at 4 ("Phase IIb follows on from the proof of concept in which several dose levels are

tested in the target population (dose-ranging studies) to define the minimally effective or non-effective dose and to decide the optimal dose, based on clinical efficacy and safety, to take to the next stage. Occasionally phases IIa and IIb are combined.”).

400. Third, a POSA would have known from the prior art and, especially, from NCT657 that the optimal dose would be in the range 0.1–1.6 mg dosed once weekly; and, in particular, that the doses tested in NCT657 were 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration), and 1.6 mg (with titration) semaglutide. A POSA would also have known that such doses, being examined in a Phase I or Phase II trial, were necessarily viewed as safe for use, and had already undergone significant preclinical review, including for toxicity and carcinogenicity. *See* Ex. 1047 (Tamimi) at 3-4 (“The purpose of [the Phase I] stage is to evaluate the safety, tolerability, pharmacodynamic (effect of the drug on the body e.g. effect on heart rate, blood pressure, electrocardiogram (ECG), etc.) and pharmacokinetic (effect of the body on the drug i.e. absorption, distribution, metabolism and excretion) effects of the tested drug. … Once the drug’s safety, pharmacokinetics and dose selection has been established in [Phase I trials in] healthy volunteers, the next step is to investigate the efficacy and safety of the drug in the target population.”); *see also generally, e.g.*, Ex. 1033 (Knudsen 2010) (describing the significant preclinical work involving liraglutide, including in mouse, rat, and minipig animal models).

401. On this background, a POSA would have recognized from NCT773 that a) it followed directly in time from NCT657, and b) it narrowed the range of semaglutide doses being tested. In the table below, I've shown the reported start and end dates of the NCT657 Phase II and NCT773 Phase I clinical trials, and the semaglutide doses used in each of NCT657 and NCT773:

NCT657 doses (start 6/2008; end 2/2009)	**NCT773 doses (start 2/2009; end 10/2009)**
0.1 mg	0.1 mg
0.2 mg	0.2 mg
0.4 mg	0.4 mg
0.8 mg	[not tested]
0.8 mg titrated	0.4, then 0.8 mg
1.6 mg titrated	0.4, then 0.8, then 1.2 mg

Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7.

402. It is apparent from this presentation that a POSA would have recognized that the three lowest doses used in each study were the same (i.e., 0.1, 0.2, and 0.4 mg, once weekly). *See* Ex. 1013 (NCT657) at 15; Ex. 1014 (NCT773) at 7. This would have led a POSA to conclude that those doses were not likely to be the focus of the ultimate optimized dose because they would lay at the beginning of the dose-response curve, and therefore likely have less than optimal benefit. *See, e.g.*, Ex. 1038 (Seino) at 4 (Fig. 1, below, showing a smooth dose response curve

where there is less than maximal, but still some, effect for the lowest doses of liraglutide, as measured by decrease in HbA1c; a POSA would have expected semaglutide to have a curve of similar shape):

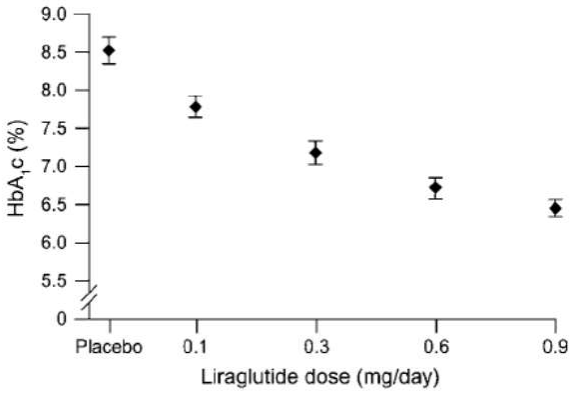

Fig. 1 – Dose–response for HbA_{1c} with increasing doses of liraglutide. Data are means ± S.E. for HbA_{1c} after 14 weeks.

403. Further, a POSA would have recognized that the "straight" 0.8 mg dose tested in NCT657 was eliminated, in favor of testing again the "titrated" 0.8 mg dose (0.8 mg reached with an initial step of 0.4 mg).

404. In addition, a POSA would have recognized that the highest doses tested in NCT773 differed from, and were lower than, the highest doses tested in NCT657. In short, the NCT773 study eliminated the titrated 1.6 mg (highest) dose used in NCT657 and replaced it with a titrated 1.2 mg dose. Ex. 1014 (NCT773) at 7. This would have led a POSA to conclude that doses lower than 1.6 mg (indeed, at or below 1.2 mg) were expected to be effective, and that the maximal response was expected to be in the range from 0.8 to 1.2 mg. It also would have suggested to a

POSA that the 1.6 mg dose was no longer a preferred or potential option because of unwanted adverse effects.

405. Finally, a POSA would have noted that the two highest doses tested in NCT773 (i.e., 0.8 mg and 1.2 mg, each with preceding steps of 0.4 mg and 0.4 and 0.8 mg, respectively) each used titration to reach the final treatment dose. From this, a POSA would have concluded that the 0.8 and 1.2 mg doses were near the final, optimized dose: the titration steps suggest an attempt to minimize the occurrence of adverse effects on the way to a presumed effective target dose.

406. In my opinion, these changes would have suggested to a POSA that the focus for semaglutide dosing was near or in the range from 0.8 to 1.2 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg, using steps of 0.1 mg (five dose amounts) or 0.2 mg (three dose amounts).

407. Therefore, in my opinion, a POSA would have been motivated by NCT657 and NCT773 to optimize the dose of semaglutide within the known range, and, separately and specifically, would have been motivated to pursue a treatment dose of 1.0 mg semaglutide once weekly to treat type 2 diabetes.

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

408. In my opinion, a POSA would have had a reasonable expectation of success optimizing the known dosing range to treat type 2 diabetes with a

semaglutide dosing regimen, and separately would have had a reasonable expectation of success treating type 2 diabetes with a dose of 1.0 mg once weekly.

409. As described earlier, a POSA would have known from the prior art that liraglutide and semaglutide shared the same amino acid backbone (i.e., the portion of the molecule that renders it effective to bind the GLP receptor), and therefore would have reasonably expected them to behave in similar fashion as GLP-1 receptor agonists. *See* Section IX.D.1.b. As further support, a POSA would have known that there were several other GLP-1-related compounds being studied, each of which was known to be effective to reduce one or more of HbA_{1c} levels, body weight, and blood glucose concentrations, while avoiding the complication of hypoglycemia, in both human and preclinical trials. *See* Ex. 1012 (Lovshin) at 2-5 (identifying, in addition to liraglutide: exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC1134, LY2199265, and LY2428757, several of which were once weekly formulations); *see also* Ex. 1035 (Lund) at 610, Table 1 (identifying, in addition to liraglutide: exenatide, exenatide once weekly, lixisenatide, CJC-1134-PC, albiglutide, and dulaglutide, several of which were once weekly formulations, two of which were launched, and four of which were in Phase III trials or expected shortly to be launched). A POSA would have reasonably expected semaglutide to behave in a generally consistent way as a GLP-1 receptor agonist, given the similarity in structure and pharmacology among the several

compounds. *See* Ex. 1032 (Knudsen 2004) at 3, Fig. 3 (showing important conserved GLP-1 residues); *id.*, Figs. 1 and 2 (GLP-1 and liraglutide sequences); Ex. 1001 ('462 patent) at 9:43-44 (citing Ex. 1015 (WO537) at 48:4-22 (Example 4) for semaglutide sequence) (Section IX.D.1.b above, showing conservation in liraglutide and semaglutide of residues known to be essential for binding); *see also* ¶¶ 77-78 above (showing nearly identical amino acid sequences for liraglutide and semaglutide); Ex. 1035 (Lund) at 610, Table 2 (showing sequence homology between GLP-1 and GLP-1 receptor agonists already on the market or in late clinical development).

410. Moreover, a POSA's knowledge related to NCT657 and NCT773, as detailed above (*see* ¶¶ 385-395), would have provided the POSA with a reasonable expectation of success given the POSA's knowledge related to clinical trial design, the teachings of NCT657 and NCT773 specifically, and the prior art detailed above in Section VIII.

411. Particularly, as described above, a POSA would have known generally from the prior art that semaglutide was being investigated in Phase I and Phase II trials to treat type 2 diabetes using a once weekly dose, and a dose in the range of 0.1–1.6 mg once weekly was the target. *See* Ex. 1012 (Lovshin) at 2 (Table 1), 5; *see also* Ex. 1035 (Lund) at 7-8 ("Semaglutide (NN9535) is a long-acting GLP-1R agonist planned for once-weekly[subcutaneous] injections, based on the GLP-1

backbone… So far, 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).”), 3 (Fig. 1) (semaglutide is a once weekly GLP-1-based treatment), 4 (Table 1) (semaglutide is a once weekly formulation in Phase II development); Ex. 1061 (’321 publication) at [0010] (“WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S.”); Ex. 1040 (Vilsbøll) at 4 (semaglutide is a “GLP-1 receptor agonist[] currently on the market or in clinical development,” in Phase II trials for once weekly dosing); Ex. 1011 (WO421) at 44:31 (“Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).”).

412. Further, based on these disclosures, and what a POSA would have known about clinical trial planning and execution, a POSA would have known that Novo Nordisk conducted the NCT657 and NCT773 phase II and I studies as dose-ranging exercises, in which the trials tested specific, selected doses to yield a dose-response curve that would, in turn, guide the selection of an optimal dose for use

with patients (i.e., one that would provide an acceptable balance between clinical benefit and adverse events).

413. A POSA also would have known from the prior art and, especially, from NCT657 that the optimal dose would be in the range 0.1–1.6 mg dosed once weekly because the semaglutide doses tested in NCT657 were 0.1, 0.2, 0.4, 0.8 mg (with titration), and 1.6 mg (with titration) once weekly. A POSA would have understood that these doses were necessarily viewed as safe for use, because they would have undergone significant preclinical review before proceeding to a Phase II trial. *See* Ex. 1047 (Tamimi) at 3-4 ("The purpose of [the Phase I] stage is to evaluate the safety, tolerability, pharmacodynamic (effect of the drug on the body e.g. effect on heart rate, blood pressure, electrocardiogram (ECG), etc.) and pharmacokinetic (effect of the body on the drug i.e. absorption, distribution, metabolism and excretion) effects of the tested drug. … Once the drug's safety, pharmacokinetics and dose selection has been established in [Phase I trials in] healthy volunteers, the next step is to investigate the efficacy and safety of the drug in the target population."); *see also generally, e.g.*, Ex. 1033 (Knudsen 2010) (describing the significant preclinical work involving liraglutide, including in mouse, rat, and minipig animal models).

414. Building on this background, a POSA would have recognized that NCT773, which followed directly in time from NCT657, narrowed the range of

semaglutide doses being tested, from 0.1 to 1.6 mg once weekly to 0.1 to 1.2 mg once weekly. The table below shows the once weekly semaglutide doses used in each of NCT657 and NCT773 (each trial used 0.1, 0.2, and 0.4 mg doses):

NCT657 doses	**NCT773 doses**
0.1 mg	
0.2 mg	
0.4 mg	
0.8 mg	[not tested]
0.8 mg titrated	0.4, then 0.8 mg
1.6 mg titrated	0.4, then 0.8, then 1.2 mg

Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7.

415. That each trial used the same three lowest doses would have led a POSA to conclude that none of those doses was likely to be the ultimate optimized dose; each would have been more likely to reside on the beginning of semaglutide dose-response curve, and would therefore likely have less than optimal benefit. *See, e.g.*, Ex. 1038 (Seino) at 4 (Fig. 1, below, showing less than maximal effect for the lowest doses of liraglutide, as measured by decrease in HbA1c):

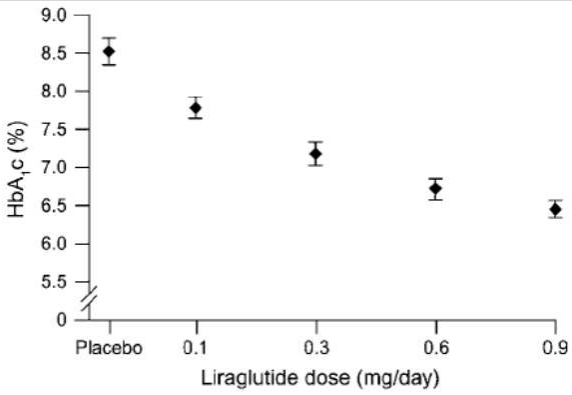

Fig. 1 – Dose–response for HbA_{1c} with increasing doses of liraglutide. Data are means ± S.E. for HbA_{1c} after 14 weeks.

416. In addition, a POSA would have recognized that the highest doses tested in NCT773 differed from, and were lower than, the highest doses tested in NCT657. In short, the NCT773 study eliminated the titrated 1.6 mg (highest) dose used in NCT657 and replaced it with a titrated 1.2 mg dose. Ex. 1014 (NCT773) at 7. This would have led a POSA to conclude that doses lower than 1.6 mg (indeed, at or below 1.2 mg) were expected to be effective, and that the maximal pharmacodynamic response would likely reside in the range from 0.8 to 1.2 mg once weekly.

417. Finally, a POSA would have noted that the two highest doses tested in NCT773 (i.e., 0.8 mg and 1.2 mg, each with preceding steps, of 0.4 mg and 0.4 and 0.8 mg, respectively) each used titration to reach the final treatment dose. From this, a POSA would have concluded that the 0.8 and 1.2 mg doses were near the final, optimized dose: the titration steps suggest an attempt to minimize the occurrence of adverse effects on the way to a presumed effective target dose.

418. Together, these many and varied supporting facts would have provided a skilled artisan with a reasonable expectation of success treating type 2 diabetes with a once weekly, 1.0 mg dose of semaglutide.

419. Therefore, in my opinion, a POSA would have had a reasonable expectation of success, based on NCT657 and NCT773, of optimizing the dose of semaglutide within the known range, and, separately and specifically, would have had a reasonable expectation of success treating type 2 diabetes with a 1.0 mg once weekly dose.

2. Claims 2 and 3 of the '462 patent would have been obvious over NCT657 in view of NCT773

420. Claim 2 of the '462 patent depends from claim 1 and recites the additional limitation that "semaglutide is administered by parenteral administration."

421. NCT657 disclosed that the semaglutide used in the relevant experimental arms of the trial was administered by "s.c. injection." Ex. 1013 (NCT657) at 15-16.

422. NCT773 disclosed that the semaglutide used in the relevant experimental arms of the trial was administered by "s.c. injection." Ex. 1014 (NCT773) at 7; *see also id.* (safety, tolerability, and pharmacokinetics profiles of semaglutide assessed "[a]fter [w]eekly [s]ubcutaneous [i]njections").

423. A POSA would have known that the reference to "s.c. injection" in each of NCT657 and NCT773 indicated the use of "subcutaneous injection."

424. As of the priority date of the '462 patent, a POSA would have known that "[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe," or by means of an infusion pump. Ex. 1034 (Knudsen patent) at 170:25-29. Therefore, a POSA would have understood that the "s.c. injection" disclosed in each of NCT657 and NCT773 is a type of parenteral administration, and that a subcutaneous injection would be a solution.

425. Thus, in addition to rendering obvious the subject matter of claim 1, NCT657 and NCT773 each further disclosed the element of claim 2 requiring that "semaglutide is administered by parenteral administration."

426. Claim 3 of the '462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs "by subcutaneous injection."[20]

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

427. NCT657 disclosed that the semaglutide used in the relevant experimental arms of the trial was administered by "s.c. injection." Ex. 1013 (NCT657) at 15-16.

428. NCT773 disclosed that the semaglutide used in the relevant experimental arms of the trial was administered by "s.c. injection." Ex. 1014 (NCT773) at 7; *see also id.* (safety, tolerability, and pharmacokinetics profiles of semaglutide assessed "[a]fter [w]eekly [s]ubcutaneous [i]njections").

429. A POSA would have known that the reference to "s.c. injection" in each of NCT657 and NCT773 indicated the use of "subcutaneous injection."

430. Thus, in addition to rendering obvious or disclosing the subject matter of claims 1 and 2, NCT657 and NCT773 each further disclosed the element of claim 3 requiring that the parenteral administration be "by subcutaneous injection."

431. It is therefore my opinion that the subject matter of claims 2 and 3 of the '462 patent would have been obvious to a POSA over NCT657 in view of NCT773.

* * * * *

432. It is therefore my opinion that claims 1-3 of the '462 patent would have been obvious over NCT657 in view of NCT773.

3. Claims 4–10 of the ’462 patent would have been obvious over NCT657 in view of NCT773 and further in view of the ’424 publication

433. It is my opinion that claims 1–3 of the ’462 patent would have been obvious over NCT657 in view of NCT773, as described above. My opinions are limited to the treatment of diabetes with subcutaneous administration of a once weekly 1.0 mg dose of semaglutide, as recited and claimed in claims 1–3 of the ’462 patent. However, I understand it is Dr. Dalby’s opinion that the ’424 publication disclosed all formulation-related elements of claims 4–10 of the ’462 patent.

434. It is therefore my opinion that claims 4–10 of the ’462 patent would have been obvious over WO421 in view of the ’424 publication for the reasons addressed in Section IX.E.1 above and by Dr. Dalby.

* * * * *

435. It is therefore my opinion that claims 1-10 of the ’462 patent would have been obvious over NCT657 in view of NCT773 and further in view of the ’424 publication.

F. No Secondary Considerations Overcome *Prima Facie* Obviousness

436. Because Patent Owner has not yet made its position known on any secondary considerations, I reserve the right to address any secondary considerations put forth by Patent Owner in any later response to this declaration or the petition it accompanies.

1. No unexpected results

437. The file history of the ’462 patent does not contain any discussion of unexpected results, nor does it contain any suggestion that the claimed 1.0 mg once weekly dose was somehow “critical.” Instead, the evidence described above demonstrates the claimed dose would have been obvious.

2. A POSA would have known there was no long-felt, unmet need for a once weekly GLP-1 receptor agonist or 1.0 mg dosing, nor was there any skepticism in the art

438. Patent Owner may assert that there was a long-felt but unmet need for a once weekly GLP-1-derived treatment. Such a need did not exist. Once weekly GLP-1 receptor agonists existed in the prior art before the application for the ’462 patent was filed, including agonists based on either GLP-1 or exendin. Ex. 1040 (Vilsbøll) at 4, Table 1.

439. Moreover, Patent Owner may assert that there was skepticism of the claimed method of treatment with semaglutide. As detailed above, the prior art provided a wealth of knowledge related to dosing and expected results from the use of semaglutide. Thus, any assertions of skepticism would not outweigh the obviousness described above.

X. RESERVATION OF RIGHTS

440. 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 this proceeding, any relevant claim

construction, in response to any expert declarations submitted on behalf of Patent Owner, or any other circumstances that may impact my opinions.

441. Moreover, during this proceeding I may rely upon documents and/or other materials produced in the proceeding, publicly available documents, and/or any documents the parties have exchanged. Additionally, I may rely on visual aids and/or demonstrative exhibits that I prepare or have 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: 3/14/2023

By: John Bantle, MD

Dr. John Bantle

EXHIBIT A

EXHIBIT A

Exhibit No.	Description
1001	U.S. Patent No. 10,335,462
1002	Prosecution history excerpts for U.S. Patent No. 10,335,462
1011	WO 2011/138421
1012	Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REV. 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
1018	Banting, *The Internal Secretion of the Pancreas,* 7 J. LAB. CLINICAL MED. 251 (1922)
1019	Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)
1020	Bydureon prescribing information (Jan. 2012)
1021	Byetta prescribing information (Oct. 2009)
1022	Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)
1023	Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003)

Exhibit No.	Description
1024	Drucker, *The Incretin System: Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes*, 368 LANCET 1696 (2006)
1025	Glaesner, *Engineering and Characterization of the Long-Acting Glucagon-Like Peptide-1 Analogue LY2189265, an Fc Fusion Protein*, 26 DIABETES/METABOLISM RSCH. & REV. 287 (2010)
1026	HARRISON'S PRINCIPLES OF INTERNAL MED., Chapter 338 (Fauci et al. eds. 17th ed. 2008)
1027	Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)
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)
1029	Jimenez-Solem, *Dulaglutide, a Long-Acting GLP-1 Analog Fused with an Fc Antibody Fragment for the Potential Treatment of Type 2 Diabetes*, 12 CURRENT OP. IN MOLECULAR THERAPEUTICS 790 (2010)
1030	Kim, *Effects of Once-Weekly Dosing of a Long-Acting Release Formulation of Exenatide on Glucose Control and Body Weight in Subjects with Type 2 Diabetes*, 30 DIABETES CARE 1487 (2007)
1031	Knudsen, *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26 DRUGS OF THE FUTURE 677 (2001)
1032	Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEMISTRY 4128 (2004)
1033	Knudsen, *Liraglutide, a GLP-1 Analogue to Treat Diabetes*, *in* ANALOGUE-BASED DRUG DISCOVERY II (Fischer & Ganellin eds. 2010)

Exhibit No.	Description
1034	U.S. Patent No. 6,268,343 ("Knudsen patent")
1035	Lund, *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OP. ON EMERGING DRUGS 607 (2011)
1036	Mojsov, *Insulinotropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLIN. INVEST. 616 (1987)
1037	Nielsen, *Pharmacology of Exenatide (Synthetic Exendin-4): A Potential Therapeutic for Improved Glycemic Control of Type 2 Diabetes*, 117 REGUL. PEPTIDES 77 (2004)
1038	Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)
1039	*Victoza*, PHYSICIANS' DESK REFERENCE (65th ed. 2010)
1040	Vilsbøll, *Glucagon-Like Peptide-1 and Diabetes Treatment*, 21 INTERNATIONAL DIABETES MONITOR 1 (2009)
1041	WO 03/002136
1042	WO 91/11457
1047	Tamimi, *Drug Development: From Concept to Marketing!*, 113 NEPHRON CLINICAL PRAC. c125 (2009)
1057	WO 2011/073328
1061	U.S. Patent Application Pub. No. US2011/0166321
1062	Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364 NEW ENGL. J. MED. 852 (2011)

Exhibit No.	Description
1063	Kirillova, *Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?*, 7(6) PLoS ONE 1 (2012)
1064	Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)
1065	Tasneem, *The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty*, 7(3) PLoS ONE 1(2012)
1076	*ClinicalTrials.gov Background*, CLINICALTRIALS.GOV, https://clinicaltrials.gov/ct2/about-site/background (last visited Mar. 10, 2023)
1077	*Award: ClinicalTrials.gov*, https://ash.harvard.edu/news/clinicaltrials.gov (last visited Mar. 10, 2023)
1079	*NCT00167115*, CLINICALTRIALS.GOV, https://www.clinicaltrials.gov/ct2/show/NCT00167115 (last visited Mar. 10, 2023)
1080	*NCT01933490*, CLINICALTRIALS.GOV, https://www.clinicaltrials.gov/ct2/show/NCT01933490 (last visited Mar. 10, 2023)