

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

**IN RE: OZEMPIC (SEMAGLUTIDE)
PATENT LITIGATION**

No. 22-md-3038-CFC

**NOVO NORDISK INC. and NOVO
NORDISK A/S,**

No. 22-cv-294-CFC
CONSOLIDATED
ANDA CASE

Plaintiffs/Counterclaim
Defendants,

v.

RIO BIOPHARMACEUTICALS INC. et al.,

Defendants/Counterclaim
Plaintiffs.

**NOVO NORDISK INC. and NOVO
NORDISK A/S,**

No. 22-cv-1040-CFC
ANDA CASE

Plaintiffs/Counterclaim
Defendants,

v.

MYLAN PHARMACEUTICALS INC.,

Defendant/Counterclaim
Plaintiff.

**Opening Expert Report of Dr. John Bantle
Regarding Invalidity of U.S. Patent No. 10,335,462**

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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
U.S. Patent No. 10,335,462 NN-OZEM-000000071-95	'462 patent
U.S. Patent No. 10,335,462 file history NN-OZEM-000003820-4446	'462 file history
U.S. Patent No. 5,512,549	'549 patent
U.S. Patent No. 8,114,833 SEMA(JDG)_0000447-468	'833 patent
Banting, <i>The Internal Secretion of the Pancreas</i> , 7 J. LAB. CLINICAL MED. 251 (1922)	Banting
Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)	Bell
Bhansali, <i>Historical Overview of Incretin Based Therapies</i> , 58 J. ASSOC. OF PHYSICIANS OF INDIA 10 (2010) SEMA(JDG)_0000014-18	Bhansali
Highlights of Prescribing Information: Bydureon, Rev. 1/2012 https://www.accessdata.fda.gov/drugsatfda_docs/label/2012/022200Orig1s0001bledt.pdf (last accessed Feb. 26, 2024)	Bydureon label
Highlights of Prescribing Information: Byetta, Rev. 10/2009 https://www.accessdata.fda.gov/drugsatfda_docs/label/2009/021773s9s11s18s22s251bl.pdf (last accessed Feb. 26, 2024)	Byetta label
<i>ClinicalTrials.gov Background</i> , CLINICALTRIALS.GOV, https://clinicaltrials.gov/about-site/about-ctg (last visited Mar. 15, 2024)	ClinicalTrials.gov Background

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Drab, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects</i> , 30 PHARMACOTHERAPY 609 (2010)	Drab
Drucker, <i>Enhancing Incretin Action for the Treatment of Type 2 Diabetes</i> , 26 DIABETES CARE 2929 (2003)	Drucker 2003
Drucker, <i>The Incretin System: Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes</i> , 368 LANCET 1696 (2006)	Drucker 2006a
Drucker, <i>The Biology Of Incretin Hormones</i> , 3 CELL METABOLISM 153 (2006)	Drucker 2006b
Glaesner, <i>Engineering and Characterization of the Long-Acting Glucagon-Like Peptide-1 Analogue LY2189265, an Fc Fusion Protein</i> , 26 DIABETES/METABOLISM RSCH. & REV. 287 (2010)	Glaesner
HARRISON'S PRINCIPLES OF INTERNAL MED., Chapter 338 (Fauci et al. eds. 17th ed. 2008)	Harrison's
<i>Award: ClinicalTrials.gov</i> , https://ash.harvard.edu/news/clinicaltrials.gov (last visited Mar. 15, 2024)	Harvard Award
Holst, <i>Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut</i> , 211 FEBS LETTERS 169 (1987)	Holst 1987
Holst, <i>Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus</i> , 4 CURRENT OP. IN PHARMACOLOGY 589 (2004)	Holst 2004
Jimenez-Solem, <i>Dulaglutide, a Long-Acting GLP-1 Analog Fused with an Fc Antibody Fragment for the Potential Treatment of Type 2 Diabetes</i> , 12 CURRENT OP. IN MOLECULAR THERAPEUTICS 790 (2010)	Jimenez-Solem
Kim, <i>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</i> , 30 DIABETES CARE 1487 (2007) SEMA(JDG)_0002583-2589	Kim

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26 DRUGS OF THE FUTURE 677 (2001)	Knudsen 2001
Knudsen, <i>Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47 J. MED. CHEMISTRY 4128 (2004)	Knudsen 2004
Knudsen, <i>Liraglutide, a GLP-1 Analogue to Treat Diabetes in ANALOGUE-BASED DRUG DISCOVERY II</i> (Fischer & Ganellin eds. 2010)	Knudsen 2010a
Knudsen, <i>Liraglutide: The Therapeutic Promise from Animal Models</i> , 64 INT’L J. CLINICAL PRACTICE 4 (2010)	Knudsen 2010b
U.S. Patent No. 6,268,343 SEMA(JDG)_0000487-624	Knudsen patent
Lovshin, <i>Incretin-Based Therapies for Type 2 Diabetes Mellitus</i> , 5 NATURE REV. ENDOCRINOLOGY 262 (2009) SEMA(JDG)_0002250-58	Lovshin
Lund, <i>Emerging GLP-1 Receptor Agonists</i> , 16 EXPERT OP. ON EMERGING DRUGS 607 (2011)	Lund
Madsbad, <i>An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists—Available Efficacy and Safety Data and Perspectives for the Future</i> , 13 DIABETES, OBESITY & METABOLISM 394 (2011) SEMA(JDG)_0002439-52	Madsbad
Marre, <i>GLP-1 Receptor Agonists Today</i> , 93 DIABETES RSCH. & CLINICAL PRAC. 317 (2011)	Marre
Mojsov, <i>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</i> , 79 J. CLIN. INVEST. 616 (1987)	Mojsov
Monami, <i>Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis</i> , 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)	Monami

TABLE OF ABBREVIATIONS
(continued)

Full Name of Cited Reference	Abbreviation
NCT00167115, CLINICALTRIALS.GOV, https://www.clinicaltrials.gov/ct2/show/NCT00167115 (last visited Mar. 15, 2024)	NCT00167115
NCT01933490, CLINICALTRIALS.GOV, https://www.clinicaltrials.gov/ct2/show/NCT01933490 (last visited Mar. 15, 2024)	NCT01933490
Clinical Trial No. NCT00696657	NCT00696657
Clinical Trial No. NCT00851773	NCT00851773
Nielsen, <i>Pharmacology of Exenatide (Synthetic Exendin-4): A Potential Therapeutic for Improved Glycemic Control of Type 2 Diabetes</i> , 117 REGUL. PEPTIDES 77 (2004)	Nielsen
Novo Nordisk Pipeline – Semaglutide (2010-2011) http://novonordisk.com:80/science/pipeline/rd_pipeline.asp?showid=7 (Internet Archive captures)	Novo Pipeline
Seino, <i>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</i> , 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)	Seino
Tamimi, <i>Drug Development: From Concept to Marketing!</i> , 113 NEPHRON CLINICAL PRACTICE c125 (2009)	Tamimi
Tasneem, <i>The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty</i> , 7(3) PLoS ONE 1 (2012)	Tasneem
Victoza, PHYSICIANS' DESK REFERENCE (65th ed. 2011)	Victoza label
Vilsbøll, <i>Glucagon-Like Peptide-1 and Diabetes Treatment</i> , 21 INTERNATIONAL DIABETES MONITOR 1 (2009)	Vilsbøll
Int'l Patent Application Pub. No. WO 03/002136 SEMA(JDG)_0000373-422	WO '136
Int'l Patent Application Pub. No. WO 2011/058193	WO '193
Int'l Patent Application Pub. No. WO 2011/073328	WO '328

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Full Name of Cited Reference	Abbreviation
Int'l Patent Application Pub. No. WO 2011/138421 SEMA(JDG)_0002087-2158	WO '421
Int'l Patent Application Publication No. WO 91/11457	WO '457
Int'l Patent Application Pub. No. WO 2006/097537 SEMA(JDG)_0002453-2528	WO '537
Zarin, <i>The ClinicalTrials.gov Results Database—Update and Key Issues</i> , 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., Dr. Reddy's Laboratories, Ltd. and Dr. Reddy's Laboratories, Inc., Rio Biopharmaceuticals Inc. and EMS S/A; Sun Pharmaceutical Industries Ltd. and Sun Pharmaceutical Industries, Inc.; and Zydus Worldwide DMCC, Zydus Pharmaceuticals (USA) Inc., and Zydus Lifesciences Limited (collectively, "defendants"), to provide my expert opinions regarding the invalidity of the asserted claims of U.S. Patent No. 10,335,462 ("462 patent"), which I understand to be claims 1, 3, 4, 5, and 7.

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.);
- *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
- *Mylan Pharmaceuticals Inc. v. Novo Nordisk A/S*, No. IPR2023-00724 (P.T.A.B.).

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

B. Basis for Opinions and Materials Considered

10. Exhibit B includes a list of the materials I considered, in addition to my experience, education, and training, to provide the opinions contained in this report.

C. Retention and Compensation

11. Defendants 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 report, 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 anticipated by or obvious over the following references or combinations of references:

a) WO '421 anticipated claims 1-3 of the '462 patent;

- b) NCT00696657 anticipated claims 1 and 3 of the '462 patent;
- c) Lovshin anticipated claims 1 and 3 of the '462 patent;
- d) Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537, and/or Lovshin, optionally in view of one or more of the '833 Patent and Madsbad;
- e) Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 Patent;
- f) Claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious over WO '537 in view of Lovshin.

14. As detailed below, WO '421, NCT00696657, and Lovshin disclosed all the limitations recited in claims 1 and 3 of the '462 patent.

15. However, to the extent the Court in this case finds that WO '421, NCT00696657, and Lovshin each did not anticipate claims 1 and 3 of the '462 patent, then, in light of the state of the art, WO '421, NCT00696657, WO '537, and Lovshin each would have rendered obvious claims 1, 3, 4, 5, and 7 of the '462 patent because each reference 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 doing so, alone or in view of the '833 patent and Madsbad.

16. Additionally, both WO '421 in view of the '833 patent and WO '537 in view of Lovshin 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 doing so, rendering obvious claims 1, 3, 4, 5, and 7 of the '462 patent.

17. I understand that defendants' expert Dr. Paul Dalby is submitting an expert report and offering his opinions that it would have been obvious over the prior art for a POSA to formulate semaglutide as claimed in dependent claims 4, 5, and 7 of the '462 patent. I defer to Dr. Dalby's opinions regarding the obviousness of these claims of the '462 patent.

18. Finally, it is my opinion that the '462 patent is invalid for a lack of adequate written description of the subject matter claimed in claims 1, 3, 4, 5, and 7 because the patent specification does not inform a person of ordinary skill in the art that the inventors actually possessed 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.

19. I understand that Plaintiffs Novo Nordisk Inc. and Novo Nordisk A/S may present expert opinions regarding "secondary considerations" of nonobviousness of the method of treatment claims, and/or of other claims, in response to my report, 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 Plaintiffs' experts may raise.

III. LEGAL STANDARDS

20. To prepare and form my opinions set forth in this report, 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.

21. I have been informed that the defendants bear the burden of proving invalidity by clear and convincing evidence. I have been told that this means the Court, considering the evidence, must have an abiding conviction that it is highly probable that the asserted claims are invalid.

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 invalidity, which I set forth here. By setting forth these legal standards, here and below, 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.

22. I understand that my opinions regarding invalidity 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.

23. 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.

24. 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 nonobviousness.

25. 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.

26. I understand that there is a presumption of obviousness where a claimed invention overlaps with or falls within a range disclosed in the prior art.

27. I understand that for a patent to be valid, the patent specification must contain a written description of the claimed invention.

28. I understand that determining whether a patent specification contains an adequate written description of the invention requires an objective inquiry into the complete specification from the perspective of a person of ordinary skill in the art. Based on that inquiry, the specification must describe the invention in a way understandable to the person of ordinary skill in the art and show that the inventor actually invented the invention claimed.

29. I understand that a specification does not provide an adequate written description of the invention if it only renders the claimed invention obvious when considering the provided description.

IV. PERSON OF ORDINARY SKILL IN THE ART

30. 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 invalidity if the Court adopts, or the parties agree to, a different definition of a skilled artisan.

31. The subject matter of claims 1, 3, 4, 5 and 7 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/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.

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

33. 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.

34. I understand that Plaintiffs proposed that a person of ordinary skill in the art would have, among other possible qualifications, an M.D., Ph.D. or equivalent degree in Pharmacology, Pharmaceutics, Biopharmaceutics, or a related field, and 3-5 years of experience conducting clinical research in the field of diabetes treatments, including the design of dosing regimens and dosage forms for type 2 diabetes treatments, or 3-5 years of research or industry experience relating to developing pharmaceutical formulations.

35. As explained in this report 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 regardless of which party's definition is adopted.

36. Further, regardless of which party's definition is adopted for a person of ordinary skill in the art, my opinions would not change.

V. THE '462 PATENT AND ITS ASSERTED CLAIMS

37. 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.

38. 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 Plaintiffs later assert and/or prove that the claims are entitled to an earlier priority or invention date, I reserve the right to supplement this report.

A. The '462 patent's asserted claims

39. 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.

40. Dependent claims 2, 3, 4, 5, 6, and 7² depend from claim 1, directly or indirectly, and are provided below.

41. Dependent claim 2 recites:

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

² I understand that Plaintiffs do not assert dependent claims 2 and 6 against the defendants. I recite claims 2 and 6 here, however, because I understand that they provide context for asserted claims 3 and 7, respectively.

42. Dependent claim 3 recites:³

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

43. 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.

44. Dependent claim 5 recites:

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

45. Dependent claim 6 recites:

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

46. Dependent claim 7 recites:

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

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

B. The Prosecution History of the '462 Patent

47. 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.

'462 File history at NN-OZEM-000003828 (patent specification as filed).⁴

⁴ For a cited document that is a journal article, book chapter, or international patent application publication, or similar, the cited page number refers to the internal page number. For an issued U.S. patent or published U.S. patent application publication, the citation is in column:line or [paragraph] format, respectively.

48. 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: NCT00696657 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* '462 File history at NN-OZEM-000004354-57 (July 23, 2018 Office Action).

49. 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 '462 File history at NN-OZEM-000004384 (January 23, 2019 Response to Office Action (cleaned up)).

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

1. (Currently Amended) 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

~~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.~~

'462 File history at NN-OZEM-000004384 (January 23, 2019 Response to Office Action (full redline)).

51. 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 '462 File history at NN-OZEM-000004389

(February 28, 2019 Terminal disclaimer); *id.* at NN-OZEM-000004359 (July 23, 2018 Office Action describing U.S. Patent No. 9,764,003).

52. 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 [sic] 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 '462 File history at NN-OZEM-000004402-3 (March 6, 2019 Notice of Allowability).

53. The Examiner did not further consider the prior art or whether it would have anticipated or rendered obvious the amended claims. While the Examiner stated that NCT00696657 “does not teach or disclose” 1 mg semaglutide, the Examiner did not consider whether NCT00696657 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.

54. Further, while the Examiner expressly mentioned NCT00696657 as being “[t]he closest prior art to the instant claims,” ’462 File history at NN-OZEM-000004402 (March 6, 2019 Notice of Allowability), the Examiner never considered that art in a substantive obviousness rejection against the issued claims.

55. Based on my review of the ’462 patent’s prosecution history, the Patent Office did not substantively apply much of the prior art described in my report against the issued claims of the ’462 patent. This includes WO ’421, WO ’537, the ’833 patent, and Lovshin, which alone or together disclosed a once weekly, 1 mg dose of semaglutide to treat type 2 diabetes. *See generally* ’462 file history, including at NN-OZEM-000004349-60 (July 13, 2018 Office action asserting rejections under 35 U.S.C. § 112; anticipation rejections over NCT00696657, Madsbad, and Kim; and obviousness-type double patenting over U.S. Patent No. 9,764,003); NN-OZEM-000004399-4404 (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 NN-

OZEM-000004405 (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

56. I understand that the claims of a patent generally 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.

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

58. However, I understand that the Court issued a claim construction order on July 25, 2023, D.I. 148 in No. 22-md-3038, adopting the following construction related to the asserted claims:

U.S. Patent No. 10,335,462	
Term	Court's Construction
"A method for treating type 2 diabetes" (Claim 1)	The preamble term is an express limitation of claims 1-10, and it means that "the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes" or

	“the claimed administration is intended to care for and manage a patient with Type 2 diabetes.”
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59. I understand that the Court’s claim construction related to the method claims’ preamble does not require any particular degree of efficacy for the claimed method.

60. I further understand that the Court’s claim construction order also adopted the parties’ following agreed constructions related to the asserted claims:

CLAIM TERMS AGREED UPON IN U.S. PATENT NO. 10,335,462		
Term	Claim(s)	Construction
“once weekly in an amount of 1.0 mg”	1	Plain and ordinary meaning, which is “one administration per week in an amount of 1.0 mg”
“solution”	3, 4, 5, and 7	Plain and ordinary meaning which is “a solution comprising semaglutide”

61. I have applied these ordered and agreed claim constructions to reach my opinions in this report.

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

A. Diabetes Generally

62. Insulin is a hormone produced and secreted by the pancreatic islets, Harrison’s at 2278, 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 2275.

63. 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 2279. 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 2280. The result is high blood glucose levels. Finally, gestational diabetes affects pregnant women and is often caused by insulin resistance. *Id.* at 2276.

64. 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 2277. 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 2277, 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 2275.

B. Diabetes Treatment

65. 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) allow the patient a lifestyle as close to normal as possible. Harrison's at 2294. To reach these goals, lowering plasma glucose is a primary aim. *Id.*

66. In 1922, Dr. Fredrick Banting and Charles Best discovered that insulin was secreted by the pancreas. 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. Harrison's at 2296.

67. 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* Bell. Additional studies discovered that the body naturally synthesizes truncated forms of the GLP-1 peptide, including GLP-1 (7-37). *See, e.g.,* Mojsov; 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. Mojsov at 616-18; Holst 1987 at 172-74. 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.

68. 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. Harrison's at 2299, 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.*

69. 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 2299-2300, Tables 338-11, -12.

70. 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 2299, Table 338-11.

71. 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

72. For almost 100 years before the priority date, it was known that gut hormones are responsible for insulin secretion. *See generally* 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.

73. 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.*, '549 patent at Abstract, 1:9-11, 2:27-32, 3:9-11, 25-30; WO '457 at 2:24-29, 3:2-7. The literature repeatedly encouraged the use of these derivatives of GLP-1(7-37) for the treatment of diabetes. '549 patent at Abstract, 1:9-11, 3:9-11, 55-60; WO '457 at Abstract.

74. "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." 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.*

75. 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.

76. Interestingly, 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.*; see also Knudsen 2010a at 337-388 and Figure 14.3 (describing beneficial GLP-1 receptor agonist effects including: slowed gastric emptying, slower food processing, and reduced hunger sensations, with the result being that “a beneficial effect on body weight may be expected with

any therapeutic application of GLP-1”; and improvements in myocardial and endothelial function, resulting in increased cardioprotection), Drucker 2006b at 154 (Figure 1) (same).

D. Use of Liraglutide to Treat Diabetes

77. 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* Byetta label; Bydureon label; 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.,* Drucker 2006a; Lund; Knudsen 2010a; Victoza label; Vilsbøll.

78. Liraglutide, approved by FDA under the trade name Victoza, is “an analog of human GLP-1 and acts as a GLP-1 receptor agonist.” Victoza label at 2671; *see also* 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 acid substitution and an attachment of a C16 acyl chain, which allows the

⁵ Byetta (exenatide) was first approved in 2005. Byetta label at 1. Bydureon (exenatide extended release) was first approved in 2012. Bydureon label at 1. Victoza (liraglutide) was first approved in 2010. Victoza label at 2668.

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).

Victoza label at 2668.

79. 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. Victoza label at 2668; 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.” Victoza label at 2668 (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.*

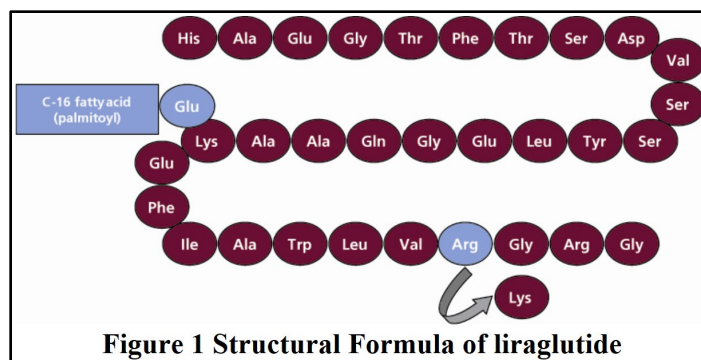
80. Liraglutide was known to reduce HbA1c effectively.⁶ See Knudsen 2010a at 348 (describing reductions in HbA1c of 0.98 to 1.45% in a 14-week

⁶ The term “HbA_{1c}” refers to glycated hemoglobin, a long-term measure of mean plasma glucose concentrations. Holst 2004 at 590.

study versus a 0.29% increase with placebo), 349 (describing reductions in HbA1c of up to 1.6% in studies lasting 26 to 52 weeks, resulting in HbA1c values below 7%), 350 (describing reduction in HbA1c of 1.12% in a 26-week study, and also reporting reduction in HbA1c of 0.79% with exenatide); *see also* Drab at 615, Table 1 (compiling liraglutide and exenatide clinical trial results and the effect of each drug on HbA1c).

81. Liraglutide was also known to reduce body weight effectively. *See* Knudsen 2010a at 349 (describing reduction in body weight of up to 3 kg in a 14-week study, statistically significant versus placebo), 349-50 (describing reductions in body weight of up to 2.5 kg in studies using liraglutide monotherapy and 3 kg when used in conjunction with certain other agents), 350 (describing reduction in body weight of 3.24 kg in a 26-week study, and also reporting reduction in body weight of 2.87 kg with exenatide); *see also* Drab at 615, Table 1 (compiling liraglutide and exenatide clinical trial results and the effect of each drug on HbA1c).

82. 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.” Victoza label at 2671. Liraglutide’s amino acid sequence, as depicted in the Victoza label, is:



*Id.*⁷

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

HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

Id.

84. 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* WO '193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)”); Bhansali at 13 (“[s]emaglutide (NN9535) is a once-weekly human GLP-1

⁷ This figure appears in the Victoza label. 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/2022/022341s037s0381b1.pdf (last accessed Feb. 26, 2024).

analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes,” which had already completed phase 2 studies; semaglutide “lowers blood glucose through stimulating release of insulin and lowers body weight”); Novo Pipeline at 1 (“Semaglutide (NN9535) is a once weekly human GLP-1 analogue, which is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin, and additionally lowers body weight.”); ’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.”); WO ’537 at 47:4-22 (Example 4); *see also* ’462 patent at 9:43-45 (admitting that WO ’537 at 47:4-22 (Example 4) discloses the semaglutide sequence and that it is “a mono-acylated GLP-1 agonist for once weekly administration”).

85. That amino acid sequence, in single-letter abbreviation is:

H[A]EGTFTSDVSSYLEGQAAKEFIAWLVRGRG

WO ’537 at 47:4-22 (Example 4)(where “[A]” represents a modified amino acid).

86. 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

87. 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, including semaglutide (as described above).

88. 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). Lund at 610, 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 609, 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 VII	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 610, Table 1.

89. 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. Indeed, as of at least July 26, 2010, Novo Nordisk was providing information about “[a] once weekly human GLP-1 analogue, semaglutide (NN9535, Novo Nordisk) (see Table 3), ... currently being developed for the treatment of [type 2 diabetes]. Semaglutide recently completed phase 2 clinical trials involving more than 400 people.” *See* Marre at 321 (citing Novo Pipeline status as of July 26, 2010); Novo Pipeline at 1-3 (Aug. 19, 2010; Nov. 25, 2010; and Jan. 27, 2011 Internet Archive captures of Novo Nordisk R&D page reporting that “[s]emaglutide (NN9535) is a once weekly human GLP-1 analogue, which is being developed by Novo Nordisk for the

treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin, and additionally lowers body weight. The phase 2 programme including more than 400 people was completed in 2009.”).

90. Dulaglutide, as one example of a long-acting GLP-1 receptor agonist, is a GLP-1/immunoglobulin G (IgG4) Fc fusion protein. Glaesner at 287; Jimenez-Solem at 790. 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.” Glaesner at 291; Jimenez-Solem at 790. 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. Glaesner at 292; Jimenez-Solem at 791-92. Similarly, dulaglutide demonstrated at least a two-fold enhancement of glucose-elicited insulin release for at least 7 days in monkeys. Glaesner at 292-93. Finally, dosing in mice demonstrated durable reductions in plasma glucose and small but statistically significant weight reduction. Glaesner at 293. Each of these effects was demonstrated to be mediated by the GLP-1 receptor. Glaesner at 293; Jimenez-Solem at 792 (“The addition of the GLP-1 receptor antagonist exendin(9-39) (1 μ M) 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.” Glaesner at 295; *see also* Jimenez-Solem at 795 (“[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.”).

91. 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, with the molecules sharing 53% amino acid sequence overlap; i.e., exenatide is not a true GLP-1 analog. Nielsen at 77. 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 79. Further, clinical trials on exenatide displayed “a consistent pattern of safety and pharmacodynamics,” including significant reductions in HbA1c. *Id.* at 80-81. 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 81. Nielsen concluded by saying that, in the face of many 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 86. As we now know, exenatide was found safe and effective and was approved by the FDA for marketing. Lund at 610, Table 1.

92. 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.” Lund at 613; *see also* Novo Pipeline 1-3. 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 613-14.

93. 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 607.

94. 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 609.

95. 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.*

96. 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 611. 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 614.

97. 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. Lovshin at 263, 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.		

98. In addition, Drab taught that “incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes.” Drab at 609. 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 617-18.

99. 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 611.

100. 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 613, 618.

101. Lovshin disclosed the benefits of using liraglutide, as well: reduction in HbA1c, reduction in fasting plasma glucose, weight loss, and reduced blood pressure. Lovshin at 264.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

102. I identify below the prior art references supporting my expert opinions on invalidity of claims 1, 3, 4, 5, and 7 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.

103. The prior art disclosures identified in this expert report would have been understood by a skilled artisan considering 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 an asserted reference for arguing invalidity, 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.

104. 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

105. 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.

106. 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.

Lovshin at 262.

107. 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 263. 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.*

108. Among the new GLP-1 agonists, Lovshin identified “NN9535,” which a POSA would have known is semaglutide. *See* WO '193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)”); Lund at 610, Table 1 (“Semaglutide (NN9535) Novo Nordisk”); WO '328 at 1:16-17 (“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.”); '462 patent at 9:43-45 (admitting that WO '537 at 47:4-22 (Example 4) discloses the semaglutide sequence and that it is “a mono-acylated GLP-1 agonist for once weekly administration”). Lovshin disclosed that NN9535 (semaglutide)

treatment was being investigated at “0.1-1.6 mg once weekly” doses as an incretin therapy. Lovshin at 263 (Table 1).

109. 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 266; *compare, e.g.*, WO ’537 at 47:4-8 (Example 4, showing the amino acid sequence and structure of semaglutide).

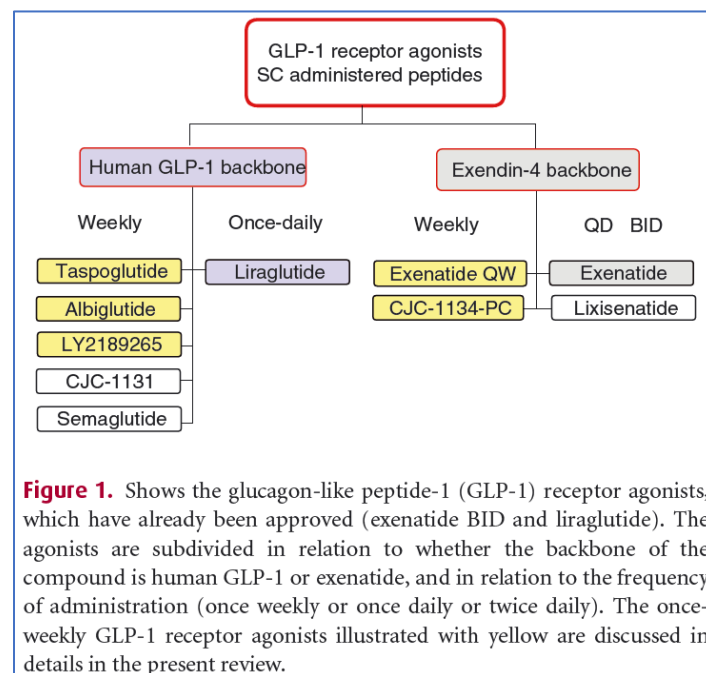
B. Madsbad

110. Madsbad et al., *An Overview of Once-Weekly Glucagon-Like Peptide-1 Receptor Agonists—Available Efficacy and Safety Data and Perspectives for the Future*, 13 DIABETES, OBESITY & METABOLISM 394 (2011) (“Madsbad”) was published in 2011. I understand that Madsbad is prior art to the claims of the ’462 patent.

111. Madsbad reviewed available and known treatments for type-2 diabetes, including several GLP-1 agonists administered once weekly. Madsbad compared these once-weekly GLP-1 receptor agonists to exenatide, which was a known GLP-1 receptor agonist dosed twice daily: “[a] greater reduction in haemoglobin A1c (HbA1c) and fasting plasma glucose was found with the once-

weekly GLP-1 receptor agonists compared with exenatide BID” and gastrointestinal side effects were less with the once-weekly agonists compared with exenatide BID,” with one exception. Madsbad at 394. According to Madsbad, “[t]he once-weekly GLP-1 receptor analogues are promising candidates for the treatment of type 2 diabetes.” *Id.*

112. In Figure 1, Madsbad disclosed GLP-1 receptor agonist dosing regimens, including once weekly subcutaneous (i.e., “(sc) administered”) dosing for semaglutide, which was known to be in a class with other once weekly GLP-1 receptor agonists:



Id. at 395.

113. Madsbad disclosed that “[i]ncretin-based therapies, such as the injectable glucagon-like peptide-1 (GLP-1) receptor agonists and orally

administered dipeptidyl peptidase-4 (DPP-4) inhibitors, have recently been introduced into clinical practice. ... Several once-weekly GLP-1 receptor agonists are in phase 3 development.” *Id.* at 394.

C. U.S. Patent No. 8,114,833

114. U.S. Patent No. 8,114,833 (“’833 patent”), entitled “Propylene Glycol-Containing Peptide Formulations which are Optimal for Production and for Use in Injection Devices,” issued on February 14, 2012. The ’833 patent identifies Novo Nordisk A/S as the assignee and the inventors as Tina Bjeldskov Pedersen, Claude Bonde, and Dorthe Kot Engelund. I understand that the ’833 patent is prior art to the claims of the ’462 patent.

115. The ’833 patent 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.” ’833 patent at Abstract.

116. The ’833 patent disclosed:

The inclusion of isotonicity agents in peptide-containing pharmaceutical formulations is widely known and one of the more common isotonic agents used in such formulations is mannitol. However, the present inventors have observed that mannitol causes problems during the production of peptide formulations as it

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

Id. at 1:30-45.

117. The '833 patent further disclosed “that peptide formulations containing propylene glycol at certain concentrations exhibit reduced deposits in production equipment and in the final product and also exhibit reduced clogging of injection devices.” *Id.* at 1:53-57.

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

119. The '833 patent 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 3:49-4:2.

120. The '833 patent 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 4:4-19.

121. And the '833 patent 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 4:20-24.

122. Among the GLP-1 peptides described by the '833 patent 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 4:25-6:2.

123. Regarding concentrations of the disclosed formulations, the '833 patent 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 8:21-26.

124. Regarding various potential components of the formulation, the '833 patent disclosed that the formulation could contain propylene glycol in various concentrations, *id.* at 10:17-31, have a pH from 7.0 to 9.5, *id.* at 10:32-43, buffer, *id.* at 10:47-57, and preservative ("well-known to the skilled person"), like phenol, *id.* at 10:58-11:9.

125. For example, the '833 patent disclosed:

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

Id. at 10:47-57 (emphasis added).

126. And further, the '833 patent disclosed:

Where a pharmaceutically acceptable preservative is to be included in the formulations of the invention, the preservative is selected from the group consisting of *phenol*, m-cresol, methyl p-hydroxybenzoate, propyl p-hydroxybenzoate, 2-phenoxyethanol, butyl p-hydroxybenzoate, 2-phenylethanol, benzyl alcohol, chlorobutanol, and thiomerosal, or mixtures thereof. . . . *In a preferred embodiment of the invention the preservative is phenol or m-cresol.*

Id. at 10:58-67 (emphasis added).

127. The '833 patent further disclosed that “[t]he use of a preservative in pharmaceutical compositions is well-known to the skilled person. *Id.* at 11:6-7.

128. The '833 also disclosed the conventional nature of its formulations and their preparation:

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

Id. at 12:64-13:3.

129. The '833 patent 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 13:4-6.

130. As to uses of such formulations, the '833 patent 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 13:30-51.

131. Further, the '833 patent taught that the disclosed peptides, in a formulation, could be dosed in an effective amount to treat the condition for which the peptide was 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 13:60-14:15.

132. Examples 1-6 of the '833 patent further disclosed the use of phenol as a preservative as well as the use of a phosphate buffer at pH within the range of 7.0-9.0. *Id.* at 15:66-22:21.

133. For instance, Example 3 in the '833 patent taught that “[i]t is believed that similar results to those obtained with the above-described propylene glycol-containing formulation would also be obtained if the pH was adjusted to 7.40, 7.70 or 7.90,” and 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 19:38-20:19.

134. Example 4 in the '833 patent disclosed a formulation containing liraglutide, disodium hydrogen phosphate buffer, sodium dihydrogen phosphate buffer, mannitol, and phenol, at pH 7.4. *Id.* at 20:21-41.

135. Example 5 in the '833 patent disclosed a composition with a pH of 7.4. *Id.* at 20:67.

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

137. The '833 patent further claims “[t]he formulation according to claim 1, wherein the pH of said formulation is about 7.0 to about 8.3.” *Id.* at 22:66-67 (claim 6).

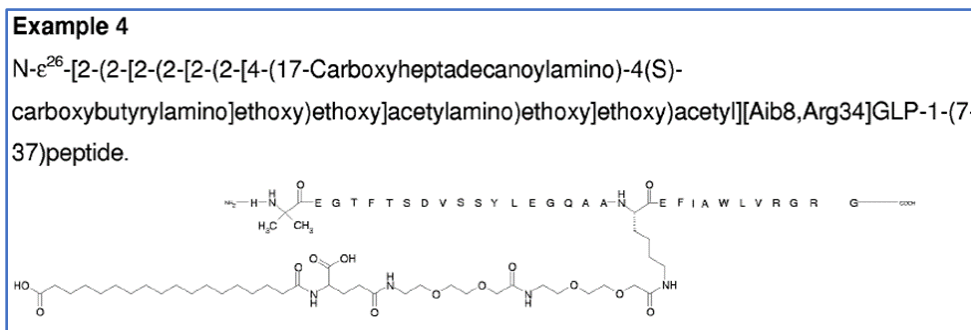
D. WO 2006/097537

138. International Patent Application Publication No. WO 2006/097537 A2 (“WO ’537”), entitled “Acylated GLP-1 Compounds,” published on September 21, 2006. WO ’537 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. I understand that WO ’537 is prior art to the claims of the ’462 patent.

139. WO ’537 disclosed “[p]rotracted GLP-1 compounds and therapeutic uses thereof. WO ’537 at cover page (abstract), 1:5-6 (“This invention relates to the field of therapeutic peptides, i.e. to new protracted GLP-1 compounds.”); *see also id.* at 4:1-3 (“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.”).

140. WO '537 disclosed the structure of semaglutide in the specification and in Claim 28:



WO '537 at 47:4-8, 73:17-75:10; *see also* '321 publication at [0010] (“WO 06/097537 disclosed 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.”); '462 patent at 9:43-45 (admitting the same).

141. WO '537 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.” WO '537 at 1:31-33.

142. WO '537 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 2:6-8;

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 5:32-35;

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 24:11-16.

143. WO '537 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 5:27-29.

144. WO '537 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 22:24–23:3.

145. WO '537 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 24:30–25:2.

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 25:4-8.

146. WO '537 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 59:24-25.

147. WO '537 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 59:28-32.

148. WO '537 also disclosed that semaglutide formulations could include “a pharmaceutically acceptable preservative,” such as phenol, and an “isotonicity agent,” like propylene glycol. *Id.* at 25:11-13, 34-35.

149. Following on this, WO '537 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 63:10-15.

150. And of course, given its subject matter, WO '537 disclosed that the semaglutide formulation could be administered parenterally, such as by subcutaneous injection. *Id.* at 34:15-16 (“Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.”).

151. WO '537 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 37:34-36.

E. WO 2011/138421

152. International Patent Application Publication No. WO 2011/138421 (“WO '421”), entitled “Combination Therapy,” published on November 10, 2011. WO '421 identified Boehringer Ingelheim International GMBH as the applicant and the inventors as Thomas Klein, Rolf Grempler, and Michael Mark. I understand that WO '421 is prior art to the claims of the '462 patent.

153. WO '421 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.

WO '421 at 1:4-9.

154. WO '421 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 decreased [sic] insulin resistance, improved measures of glycemia and lipemia, and reduced blood pressure. Maintenance [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 individuals [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 2:27-3:16.

155. WO '421 also acknowledged that GLP-1 analogues were used as diabetes monotherapy, even though WO '421 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 5:19-21.

156. WO '421 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 33:20-22.

157. WO '421 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 39:23-26.

158. In addition, WO '421 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 43:1-3 (emphasis added). WO '421 noted that “[s]emaglutide,” in particular, “is administered once weekly by subcutaneous injection (0.1-1.6 mg).” *Id.* at 43:13. 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 43:9-10.

159. Other once weekly dosage forms disclosed by WO '421 included exenatide LAR, taspoglutide, albiglutide, and dulaglutide. *Id.* at 43:7-8, 11-12, 14-15, 18-19.

F. NCT00696657 Semaglutide Clinical Trial Record

1. Clinical Trial No. NCT00696657

160. *A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide*, NCT00696657 (“NCT00696657”), is a clinical trial whose description was made available and listed on clinicaltrials.gov. According to the face of NCT00696657, certain of its details were first received by ClinicalTrials.gov on June 11, 2008. NCT00696657 at 15. Novo Nordisk was listed as the sponsor of the trial. *Id.* NCT00696657 reported that the clinical trial started in June 2008 and was completed in February 2009. *Id.* at 15. I understand that NCT00696657 is prior art to the claims of the '462 patent.

161. The official title of NCT00696657 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. NCT00696657 at 15, 17. The Brief Summary section of NCT00696657 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 HbA_{1c} and the treatment duration was 12 weeks.

Id. at 15.

162. 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. NCT00696657 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.*

163. The primary outcome measure followed in NCT00696657 was the level of HbA_{1c}, which refers to glycated hemoglobin, a long-term measure of mean plasma glucose concentrations. NCT00696657 at 15; Holst 2004 at 590.

Some secondary outcome measures in NCT00696657 included the percentage of subjects with an adverse event or hypoglycemic episode, among others. NCT00696657 at 15.

164. Christine B. Jensen, M.D., Ph.D., of Novo Nordisk A/S is listed as the study director for NCT00696657. *Id.* at 17. Christine Bjoern Jensen is listed as the named inventor on the '462 patent. *See* '462 patent at cover page item (72).

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

165. ClinicalTrials.gov is a website, maintained by the National Library of Medicine at the National Institutes of Health, that “provide[s] information about clinical research studies to the public, researchers, and health care professionals.” ClinicalTrials.gov Background at 1.

166. 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 launched and became publicly accessible in 2000. *See* ClinicalTrials.gov Background at 5. Clinicaltrials.gov was created under the Act “to create a database of clinical trials that have an investigational new drug (IND) application to test investigational drugs for serious or life-threatening diseases,” before it went live to the public in 2000. ClinicalTrials.gov Background at 5-6.

167. 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* 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.'" Harvard Award at 2.

168. 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 countries⁸ 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.

Harvard Award at 2-3 (emphasis added).

169. 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

⁸ According to ClinicalTrials.gov, this number is now "over 200 countries."

ClinicalTrials.gov Background at 1.

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.

170. That a POSA would have recognized the authoritative, accessible nature of ClinicalTrials.gov, at least because of its reliable information and readily 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.,* Zarin at 853 (“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)); 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); 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.”).

171. 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 NCT00696657.

172. 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* NCT00167115. 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. *Id.* 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* NCT01933490. In Clinicaltrials.gov, that trial is listed as “First Posted: September 2, 2013,” and “Last Update Posted: November 1, 2019.” *Id.* 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.

173. Similarly, NCT00696657 and NCT00851773 are archived versions of the ClinicalTrials.gov pages for the respective clinical trials, as retrieved and stored by the Internet Archive's Wayback Machine service.⁹ These Exhibits

⁹ I understand that the Patent Office's Manual of Patenting Examining Procedure discusses the Wayback Machine and considers that "[p]rior 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" 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

reflect the information that would have been available to a POSA on the ClinicalTrials.gov website for each clinical trial at least as of the date the page 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.*, NCT00851773 at 7 (last updated on July 15, 2010), 11 (last updated on 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.

174. 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

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 Feb. 21, 2024).

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 9 *supra*).

175. 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.

G. Other Technical Background Forming the POSA's Knowledge

176. 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. Clinical Trial No. NCT00851773

177. *Safety, Tolerability, and Profile of Action of Drug in the Body of NN9535 in Healthy Male Japanese and Caucasian Subjects*, NCT00851773 ("NCT00851773"), is a clinical trial whose description was made available and

listed on clinicaltrials.gov.¹⁰ According to the face of NCT00851773, certain of its details were first received by clinicaltrials.gov on February 25, 2009. NCT00851773 at 11. Novo Nordisk is listed as the sponsor of the trial. *Id.* at 8. I understand that NCT00851773 is prior art to the claims of the '462 patent.

178. The official title of NCT00851773 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. NCT00851773 at 7, 9. The Brief Summary section of NCT00851773 generally describes the purpose 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.

¹⁰ Consistent with the operation of clinicaltrials.gov, several versions of NCT00851773 were published and publicly available on ClinicalTrials.gov due to its regularly being updated by the trial sponsor, Novo Nordisk.

179. 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). NCT00851773 at 7.¹¹ 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.

180. The primary outcome measure followed in NCT00851773 was the incidence of adverse events at each scheduled visit. NCT00851773 at 7. Some secondary outcome measures in NCT00851773 included the frequency of

¹¹ NCT00851773 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 mg (with titration) and 1.2 mg (with titration) dosing regimens were administered.

hypoglycemic episodes, patient vital signs, and antibody development against semaglutide, among others. *Id.*

181. As can be seen in NCT00851773, several versions of the protocol were publicly available over time and were viewable to the public. For instance, the September 11, 2009 Internet Archive capture of the NCT00851773 protocol (showing a “last updated” date of “August 26, 2009”) had seven experimental arms (labeled A-G), in which once weekly subcutaneous (“s.c.”) injections of semaglutide (“NN9535”) were given at doses of 0.1 mg (arm A); 0.2 mg (arm B); 0.4 mg (arm C); 0.8 mg (with titration of “0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks”) (arm D); 0.8 mg (arm E); 1.6 mg (with titration of “0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.6 mg once weekly for 6 weeks”) (arm F); and a titration to a six-week “[d]ose to be determined based on safety and tolerability of previous dose steps,” where the “dose-arm is optional and will only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” (arm G). *Id.* at 11.

182. The August 26, 2009 update of NCT00851773 also included seven placebo comparator arms providing once weekly subcutaneous injections of placebo versions of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration as above), 0.8 mg, 1.6 mg (with titration as above), and a “[d]ose to be determined based on

safety and tolerability of previous dose steps” (with titration as above) (arms H1 through H7, respectively). *Id.* at 11-12.

183. The October 22, 2011 Internet Archive capture of the NCT00851773 protocol (showing a “last updated” date of “July 15, 2010”), had just five experimental arms, in which once weekly subcutaneous (“s.c.”) injections of semaglutide (“NN9535”) were given at doses of 0.1 mg (arm A); 0.2 mg (arm B); 0.4 mg (arm C); 0.8 mg (with titration of “0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks”) (arm D); and 1.2 mg (with titration of “0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.2 mg once weekly for 6 weeks”) (arm E). *Id.* at 7. Thus, the July 15, 2010 update of the protocol removed from the earlier trial the experimental arms providing a 0.8 mg dose and a 1.6 mg dose (used with titration), and added a lower maximum dose (1.2 mg with titration). The July 15, 2010 update of NCT00851773 similarly had five placebo comparator arms (down from the earlier seven), providing once weekly subcutaneous injections of placebo versions of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration as above), and 1.2 mg (with titration as above) (arms F1 through F5, respectively). *Id.* at 7-8. As with the experimental arms, the July 15, 2010 update of the protocol removed from the earlier trial the placebo arms testing versions of the 0.8 mg dose and the 1.6 mg dose (with titration as above), and added a lower maximum dose (1.2 mg with titration).

184. When comparing the August 26, 2009 update of NCT00851773 to the July 15, 2010 update of NCT00851773, two dosing changes are apparent. First, the July 15, 2010 update eliminated the dose of 1.6 mg (with titration of “0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.6 mg once weekly for 6 weeks”) (arm F), leaving 0.8 mg and 0.8 mg (with titration) as the highest of the originally-tested doses. Second, the July 15, 2010 update implemented a 1.2 mg (with titration) as the uppermost “[d]ose to be determined based on safety and tolerability of previous dose steps.” A POSA would have inferred from these changes, in the context of NCT00696657 (described further, below), that there were underlying concerns or cautions about the tolerability of the highest doses in each trial (0.8 mg and above) because in each case those doses were always implemented with titration being either an alternative (0.8 mg dose) or a requirement (1.2 mg and 1.6 mg doses).¹²

¹² NCT00696657 tested 0.8 mg as a standalone dose, and both 0.8 mg and 1.6 mg with titration (NCT00696657 at 7-8, 11-12, 15-16, 19, 23, 27, 31, 35, 39), and the various versions of NCT00851773 tested each of 0.8 mg, 1.2 mg, and 1.6 mg with titration (NCT00851773 at 7, 11), with the standalone 0.8 mg dose appearing once (NCT00851773 at 11).

2. *Bhansali*

185. Bhansali, *Historical Overview of Incretin Based Therapies*, 58 J. ASSOC. OF PHYSICIANS OF INDIA 10 (2010) (“Bhansali”), was published in 2010. I understand that Bhansali is prior art to the claims of the ’462 patent.

186. Bhansali taught that GLP-1 is an incretin hormone playing a role in the “physiological responses ... activated following meal intake, providing neural and endocrine signals regulating the digestion, absorption and assimilation of ingested nutrients.” Bhansali at 10. Further, that “[e]xenatide is the first GLP-1 receptor agonist that has been approved for use as an adjunctive therapy to improve glycaemic control in patients with type 2 diabetes[.]” *Id.*

187. Bhansali further noted the known regulatory approval and treatment effectiveness of liraglutide at that time:

Liraglutide is the first once-daily human GLP-1 analogue. In July 2009, Victoza® (liraglutide) was approved by the European Medicines Agency (EMA) in the treatment of type 2 diabetes mellitus to achieve glycaemic control. In January 2010, the U.S. Food and Drug Association (FDA) approved Victoza® as an adjunct therapy to diet and exercise to improve glycaemic control in adults with type 2 diabetes mellitus. It has been shown in different trials that at suggested therapeutic doses of 1.2 mg and 1.8 mg, liraglutide can lower glycated haemoglobin A1c (HbA_{1c}) by 1.0-1.5% points as mono- or combination therapy in approximately two-thirds of subjects. GLP-1 receptor agonist showed a greater

effect than the DPP-4 inhibitor in reducing postprandial glucose (PPG) concentrations, a more potent effect in increasing insulin secretion and decreasing postprandial glucagon secretion, a relatively greater effect in reducing caloric intake, and it decreased the rate of gastric emptying.

Bhansali at 10.

188. Bhansali summarized how the prior art established that incretin-based therapies like GLP-1 would be useful treatment options for glycemic and body weight control: “Overall, available evidence supports the use of incretin-based therapies in diabetes patients requiring effective glycaemic and body weight control while minimising the risk of hypoglycaemia.” Bhansali at 10; *see also id.* at 12 (treatment with GLP-1 analogues showed a “reduction in body weight,” unlike treatment with DPP-4 inhibitors, which were weight neutral).

189. Bhansali noted that GLP-1 receptors appear throughout the body and that GLP-1 receptor agonists therefore have several effects:

GLP-1 receptors are expressed in the gastrointestinal tract, endocrine pancreas (α and β cells), lung, kidneys, heart and several areas of the brain (hypothalamus, nucleus of the solitary tract, area postrema).

* * *

It is shown that GLP-1(7-36) is a more potent insulin secretagogue than [gastric inhibitory polypeptide, GIP] *in vitro*. It has been shown

in both preclinical and human studies that, *in vivo*, GLP-1 can stimulate insulin secretion in a glucose-dependent manner. Other biological effects, which include inhibiting glucagon secretion, decelerating gastric emptying and reducing food intake with GLP-1, were also demonstrated.

* * *

Interestingly, GLP-1 may also have other beneficial effects that are independent from its effects on glucose metabolism. Animal studies showed that GLP-1 protected myocardial cells from ischemic and reperfusion injury, prevented endothelial dysfunction, promoted endothelium in dependent artery relaxation and increased diuresis and natriuresis. In subjects with type 2 diabetes, studies showed that GLP-1 reduced systolic blood pressure (SBP) and decreased plasma concentrations of triglyceride and plasminogen activator inhibitor (PAI-1) and brain natriuretic peptide (BNP), which are considered biomarkers of cardiovascular diseases.

Bhansali at 11 (footnotes removed).

190. Bhansali explicitly noted that long-acting versions of GLP-1 were preferred over native GLP-1 for treatment purposes, due to the latter's short half-life. Bhansali at 11 ("Because of the short plasma half-life of native GLP-1, there is a need to develop long-acting derivatives to make GLP-1 treatment clinically relevant.").

191. Bhansali described how Amylin developed exenatide, a synthetic GLP-1 receptor agonist, as a twice-daily treatment option “to improve glycaemic control in patients with type 2 diabetes.” Bhansali at 12. Bhansali noted that clinical trial results with exenatide showed that it “stimulated insulin secretion in a glucose-dependent manner, [] suppressed glucagon secretion, slowed gastric emptying[,] reduced food intake in patients with type 2 diabetes[, and] improved long-term glycaemic control.” *Id.*

192. Bhansali disclosed that the “most common adverse effects” in patients receiving exenatide “we nausea and vomiting,” but that those were “significantly reduced with step-wise dose escalation of exenatide.” Bhansali at 12.

193. Bhansali disclosed that liraglutide was known and it is “a once-daily human GLP-1 analogue, which has been developed by Novo Nordisk.” Bhansali at 12. Liraglutide was known to be an analog of human GLP-1 where “lysine at position 34 of human native GLP-1 is substituted by arginine, and a palmitic acid chain (C-16) is attached to an ϵ -amino group of lysine at position 26 via glutamate spacer,” with an overall “97% amino acid homology with the human GLP-1 peptide.” *Id.* Bhansali noted that liraglutide was approved as Victoza® in July 2009 in Europe and in January 2010 in the United States, in each case to improve or achieve glycemic control in patients with type 2 diabetes

mellitus. *Id.* In several phase 3 trials, and at the suggested therapeutic doses of 1.2 mg and 1.8 mg once daily, “liraglutide lowered HbA_{1c} by 1.0-1.5% in approximately two-thirds of patients when administered as monotherapy or in combination with other oral antidiabetic drugs.” Bhansali at 12-13.

194. As with exenatide, “[l]iraglutide was generally well tolerated,” and “[t]he most common adverse events with liraglutide treatment were related to the gastrointestinal system,” with nausea “the most frequently reported side effect.” Bhansali at 13. These adverse events were reported to be “mostly mild and occurred during the initial period of treatment.” *Id.*

195. Bhansali noted that liraglutide was superior to exenatide in diabetes-related treatment effect: “liraglutide reduced mean HbA_{1c} significantly more than exenatide with a difference of 0.33%. More patients achieved a HbA_{1c} value of less than 7% in the liraglutide group than exenatide (54% vs. 43%). Both drugs resulted in similar weight loss, and were well tolerated, but nausea was less persistent and minor hypoglycaemia less frequent with liraglutide than with exenatide (Table 3).” Bhansali at 13.

196. Bhansali further disclosed that semaglutide (also identified as NN9535) was in active development as a promising treatment for Type 2 diabetes:

Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin and lowers body weight. The phase 2 programme with more than 400 people was completed in 2009.

Bhansali at 13; *see also* Novo Pipeline at 1-3 (same, using near-identical words).

197. Bhansali summarized by noting that “available evidence indicates that unlike current antidiabetic treatments, incretin-based therapies possess great potential in offering effective glycaemic and weight control to patients with type 2 diabetes.” *Id.*

3. *Drucker 2003*

198. Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003) (“Drucker 2003”), was published in 2003. I understand that Drucker 2003 is prior art to the claims of the ’462 patent.

199. 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.” Drucker 2003 at 2929.

200. 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 2933 (citations omitted).

201. 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.*

4. *Holst 2004*

202. 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. I understand that Holst 2004 is prior art to the claims of the ’462 patent.

203. 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. Holst 2004 at 589. 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.*

204. 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 589-90.

205. 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 590 (“GLP-1-based therapy has unusually attractive potential in diabetes treatment”).

206. 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.

207. 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.*

208. 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 591.

209. 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 591.

210. 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.*

5. *Knudsen 2001*

211. 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. I understand that Knudsen 2001 is prior art to the claims of the ’462 patent.

212. Knudsen 2001 disclosed that GLP-1 has many favorable qualities making it “an obvious drug candidate for the treatment of type 2 diabetes.” Knudsen 2001 at 677. 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.*

213. 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.*

214. According to Knudsen 2001, GLP-1 “stimulates insulin release” after a meal, and “potently inhibits glucagon secretion.” *Id.* at 678. 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.*

215. 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.*

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

217. 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.*

218. 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 679.

219. 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 679-81.

220. Knudsen 2001 disclosed that a preferred GLP-1 derivative was NN2211, also known as liraglutide, and disclosed its sequence. *Id.* at 680 (Fig. 1; Table 1, compound 5), 681.

221. 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 681.

222. 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 682.

223. 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.

6. *Knudsen 2004*

224. 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. I understand that Knudsen 2004 is prior art to the claims of the ’462 patent.

225. 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. Knudsen 2004 at 4128; *see also id.* at 4132 (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.”).

226. 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 4128. 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.

227. 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 4128-29.

228. 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 completed Phase II testing at a once-daily dosing schedule. *Id.* at 4129 (Table 1).

229. 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 4130.

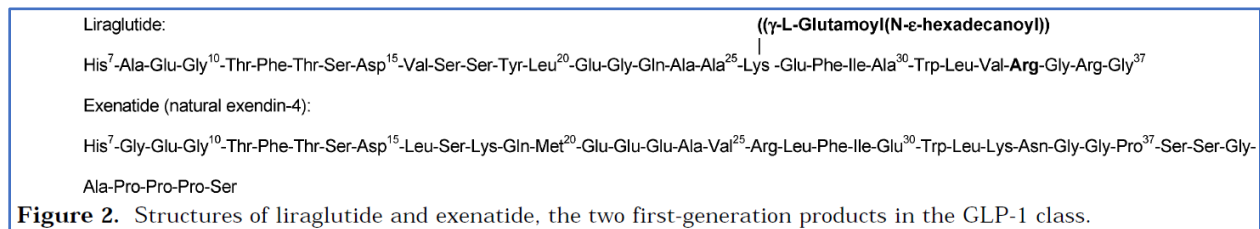
230. Summarizing information known about liraglutide, Knudsen 2004 disclosed several PK/PD characteristics, and stated that “for acylated derivatives of GLP-1[, like liraglutide,] the [structure-activity relationship] is well understood”:

Novo Nordisk has completed phase 2 clinical trials with liraglutide(γ -L-glutamoyl(*N*- α -hexadecanoyl))-Lys²⁶,Arg³⁴-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 than 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.

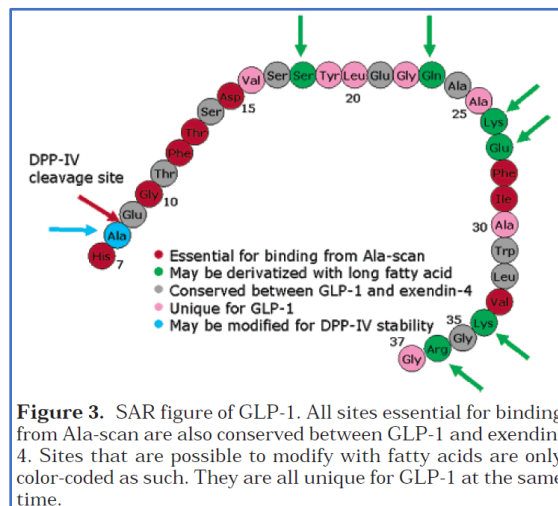
Id. (footnotes omitted).

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



Id.

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



Id.

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

234. Further, Knudsen 2004 identified what would make a successful GLP-1 drug product: “a convenient product with administration once daily or less.” *Id.* at 4131. 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.*

235. 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 4131-32. 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 4132 (footnotes omitted).

236. 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.*

7. *Knudsen patent (U.S. Patent No. 6,268,343)*

237. U.S. Patent No. 6,268,343 (“Knudsen patent”), titled “Derivatives of GLP-1 Analogs,” issued on July 31, 2001. I understand that the Knudsen patent is prior art to the claims of the ’462 patent.

238. 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.” 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.”).

239. 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.

240. The Knudsen patent further disclosed that “GLP-1 is the most potent insulintropic substance known. Unlike [glucose-dependent insulintropic 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 insulintropic 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.

241. 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.

242. Knudsen patent 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 of 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).

243. 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.

244. 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 insulintropic 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.

245. 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.

246. 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.

247. 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.

8. *Lund*

248. Lund et al., *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011) (“Lund”), was published online on September 9, 2011. I understand that Lund is prior art to the claims of the ’462 patent.¹³

249. Lund’s disclosures were described above. *See* Section VII.E.

9. *U.S. Patent Application Pub. No. US2007/0010424*

250. 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. ’424 publication at cover page. 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.

¹³ Even if 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 and Lund, as a review article, reflected what a POSA would have known as of the ’462 patent’s priority date.

251. 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.

252. 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].

253. 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].

254. 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].

255. 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].

256. 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].

257. 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].

258. 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].

259. 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 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].

260. 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].

261. 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].

262. 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.

10. *Victoza label*

263. Victoza, whose active ingredient is liraglutide, was approved by FDA in 2010, and the first approved label describing its use issued in January 2010. Victoza label at 2668. I understand that Victoza label is prior art to the claims of the '462 patent.

264. 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.* “Victoza contains liraglutide, an analog of human GLP-1” that “acts as a GLP-1 receptor agonist.” *Id.* at 2671.

265. 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 2668.

266. 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.

267. 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 2671.

268. 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 2671.

269. 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, G_s, 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 2671-72.

270. 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 2672.

11. WO 03/002136

271. International Patent Application Publication No. WO 03/002136 (“WO ’136”) is titled “Stable Formulation of Modified GLP-1,” and published on January 9, 2003. Novo Nordisk A/S is listed as the Applicant. WO ’136 at 1. The named inventors on WO ’136 are James Flink, Silke Møller Larsen, Simon Bjerregaard Jensen, and Dorthe Kot Engelund. *Id.* I understand that WO ’136 is prior art to the claims of the ’462 patent.

272. WO ’136 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 1:4-5, 3:17-30.

273. WO ’136 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.

274. And WO '136 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 2:12-20.

275. WO '136 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, intravenous [sic] or infusion) as well as non-invasive (eg nasal or pulmonary, transdermal or transmucosal e.g. buccal) means of administration.” *Id.* at 3:17-26. WO '136 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 3:32–4:14,

22:6-12, 22:29–34:29 (describing various GLP-1-related compounds and their components). WO '136 has an extensive discussion of various formulation options and uses within these parameters. *See generally id.* at 4-16.

276. Among the disclosed formulation options and uses, WO '136 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 13:29-30, 14:18-24 (“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.”).

277. WO '136 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 13:17-23.

278. WO '136 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 15:18-30.

279. Regarding the components of the described formulations, WO '136 taught that the buffer may be selected from “sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin, sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, [or] tris(hydroxymethyl)-aminomethan,” with “glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate” preferred. *Id.* at 17:27-33. WO '136 also disclosed methods for preparing the formulations which includes a step of adjusting the final pH of the formulation within the range 7.0-9.4. *Id.* at 17:20-26.

280. Regarding components of the formulation, WO '136 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 18:34-19:4. WO '136 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 18:16–21:30. The isotonic agent may be present in a concentration from 1 to 50 mg/mL. *Id.* at 19:10-11.

281. WO '136 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 23:10-12 (citing WO 98/08871, WO 99/43705, WO 99/43706, WO 99/43707, WO 99/43708, and WO 99/43341).

12. Additional prior art and references

282. 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 may cite 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 here or not, that were publicly available prior to the priority date of the '462 patent are within the scope of the prior art.

IX. INVALIDITY OF THE ASSERTED CLAIMS OF THE '462 PATENT

A. Each of WO '421, NCT00696657, and Lovshin anticipated claims 1 and 3

283. Claim 1 reads:

1. A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.

'462 patent at 35:42-44.

284. Claim 2 depends from claim 1 and adds the limitation “wherein the semaglutide is administered by parenteral administration;” claim 3 depends from claim 2 and adds the limitation “wherein the solution is administered by subcutaneous injection.” ¹⁴ *Id.* at 35:45-48.

285. I understand that the Court construed the preamble of claim 1 (“A method for treating type 2 diabetes”) to mean that “the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with

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.” '462 patent at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

Type 2 diabetes.” I further understand that the Court did not require a particular degree of efficacy for this treatment.

1. *WO '421*¹⁵

a. WO '421 anticipated claim 1

286. 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.” In my opinion, WO '421 taught each and every element of claim 1 of the '462 patent and therefore anticipated it.

287. WO '421 disclosed “[m]ethods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO '421 at 1:4-7. A POSA would have understood from this passage that a method “for the purpose of care and management of a patient with Type 2 diabetes” or “intended to care for and manage a patient with Type 2 diabetes” was disclosed, and that such method would be used with a patient in need of such treatment. This is a disclosure of

¹⁵ The content of WO '421 is also described above. *See* Section VIII.E.

the subject matter of the preamble of claim 1, which the Court ruled was limiting but did not require a particular degree of efficacy. *See* Section VI above.

288. WO '421 further disclosed that “[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide.” *Id.* at 33:20-22 (emphasis added). Finally, WO '421’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 64:27-31 (emphasis added). A POSA would have understood from this language that WO '421 disclosed a “method of treating type 2 diabetes,” and that such method would be used with a patient in need of such treatment.

289. It could be noted that WO '421 described combined administration of semaglutide and a DPP-4 inhibitor “simultaneously, separately, sequentially or chronologically staggered,” and that the described “combination therapy may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy.” *Id.* at 36:2-24; *see also id.* at 36:16-18 (“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”), 64:27-31 (claim 17).

290. However, I understand 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”). I further understand 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.

291. Thus, because claim 1 of the ’462 patent uses the transitional term “comprising” (i.e., “comprising administering semaglutide once weekly in an amount of 1.0 mg”), WO ’421’s disclosure of treatment with both semaglutide and a DPP-4 inhibitor, in which each compound may be administered “prior to, concurrent to, or subsequent to” the other, falls within the scope of claim 1 of the ’462 patent. A POSA would have understood the disclosures in these passages to include administering semaglutide alone at any point in time before or after administering a DPP-4 inhibitor, including as separate courses of treatment. Thus, from WO ’421 and other teachings in the art that semaglutide could be administered alone as a treatment for type 2 diabetes, a POSA reading WO ’421 would have immediately envisioned administering semaglutide alone.

292. Further, 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, e.g.*, Drucker 2003 at 2934 (DPP-IV inhibitors are “[o]rally available,” while GLP-1 receptor agonists are “[i]njectable”); Drucker 2006a at 1698, table (DPP-4 inhibitors are administered orally and incretin mimetics like liraglutide and exenatide are administered subcutaneously); Holst 2004 at 593 (DPP-4 inhibitors are administered orally, while GLP-1 analogs require parenteral administration). Because WO ’421’s broad definition of “combination therapy,” *id.* at 35:9-15, includes, for example, administering semaglutide alone, WO ’421 disclosed the “comprising administering semaglutide” limitation in claim 1 of the ’462 patent.

293. WO ’421 also disclosed that, for the treatment of type 2 diabetes, “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. WO ’421 at 35:23-36:5, 43:13; *see also id.* at 65:27-31 (claim 17, reciting administering a GLP-1 receptor agonist in a method of treating type 2 diabetes).

294. A POSA would have understood that WO ’421’s disclosed range of 0.1 to 1.6 mg semaglutide doses included a discrete dose of 1.0 mg. A POSA would not have viewed the disclosed range of doses in WO ’421 (“0.1-1.6 mg”)

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

295. First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram (i.e., dosing increments for Victoza were in increments of 0.6 mg (i.e., 0.6 mg, 1.2 mg, 1.8 mg). *See* Victoza label at 2668.

296. Second, a POSA would have known that semaglutide was being tested in clinical trials before the priority date, including those using once weekly subcutaneous administration of semaglutide. *See, e.g.*, NCT00696657 at 15-16, NCT00851773 at 7. A POSA would have known that in NCT00696657, semaglutide was tested at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 1.6 mg (“1.6 mg with titration”) (*e.g.*, NCT00696657 at 15-16), and that in NCT00851773,¹⁶ semaglutide was tested at doses of 0.1, 0.2, and 0.4 mg, 0.8 mg

¹⁶ My citation to the dosing step sizes disclosed by NCT00851773 is confirmatory of the step sizes disclosed by NCT00696657 because the smallest

with titration, and 1.2 mg with titration (NCT00851773 at 7). Thus, the smallest dose step size used with semaglutide was 0.1 mg, and the range of doses disclosed in WO '421 would include, at most, 16 options for dosing and a POSA would have immediately envisioned all the options in that range at the smallest reasonable step size. Therefore, WO '421's disclosure of 0.1 mg to 1.6 mg of semaglutide administered weekly anticipated the use of 1.0 mg semaglutide administered once weekly claimed in the '462 patent.

297. Thus, on dosing, a POSA would have viewed the disclosed range of doses in WO '421 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).

298. 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

dose step size used in each study was 0.1 mg and steps were designated in even tenths of a milligram. My opinions related to the disclosed step size and the number of dose options a POSA would envision would remain the same without citation to NCT00851773.

mg to 1.6 mg) of semaglutide administered weekly in the specification of WO '421 anticipated the use of 1.0 mg semaglutide administered once weekly.

299. For another reason, a POSA would have immediately envisioned a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because a POSA would have understood that doses within the disclosed range of 0.1-1.6 mg were likely to be effective, particularly doses at the upper end of the range. *See* NCT00696657, NCT00851773 (as of the priority date, semaglutide had been the subject of at least two Phase I and Phase II clinical studies with dose ranges going from 0.1 mg up to, at most, 1.6 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, including 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).^{17,18}

¹⁷ Although I conclude that a POSA would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court's claim construction requires because it does not require showing a particular degree of efficacy.

¹⁸ My analysis of what NCT00851773 taught a POSA is not essential to my opinion that WO '421 anticipated claims 1 and 3. NCT00851773's teachings just confirm that WO '421 anticipated claims 1 and 3.

300. Therefore, WO '421 disclosed administering semaglutide once weekly in an amount of 1.0 mg.

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

302. Thus, in my opinion, WO '421 disclosed all elements of claim 1 of the '462 patent and therefore anticipated it.

b. WO '421 anticipated claim 3

303. Regarding the requirement of claim 2 that “semaglutide is administered by parenteral administration” and the requirement of claim 3 that

the parenteral administration occurs “by subcutaneous injection,” WO ’421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. *Id.* at 35:23-36:5, 43:13. And, as of the priority date of the ’462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump (*see, e.g.*, Knudsen patent at 170:25-29), making “subcutaneous injection” disclosed in WO ’421 a type of parenteral administration of a solution.

304. Thus, in my opinion, WO ’421 disclosed the subject matter of claims 2 and 3 for all the same reasons described above and with respect to claim 1 and therefore anticipated claim 3.

2. *NCT00696657*¹⁹

a. NCT00696657 anticipated claim 1

305. 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.” In my opinion, NCT00696657 taught each and every element of claim 1 of the ’462 patent and therefore anticipated it.

¹⁹ The content of NCT00696657 is also described above. *See* Section VIII.F.

306. NCT00696657 disclosed a Phase 2 interventional trial wherein participants with type 2 diabetes mellitus “were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD).” NCT00696657 at 15. This is a disclosure of the subject matter of the preamble of claim 1, which the Court ruled was limiting but did not require a particular degree of efficacy. *See* Section VI above.

307. In one of the arms of the trial disclosed by NCT00696657, semaglutide was used as a treatment for diabetes with “0.8 mg with titration, once weekly, [subcutaneous] injection.” NCT00696657 at 16. In a different arm of the trial, semaglutide was used as a treatment for diabetes with “1.6 mg with titration, once weekly, [subcutaneous] injection.” *Id.* The trial included treatment with semaglutide at six different dosages, including 0.8 mg and 1.6 mg. *See id.* at 15-16.

<u>Arms</u>	<u>Assigned Interventions</u>
A: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.1 mg, once weekly, s.c. injection
B: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.2 mg, once weekly, s.c. injection
C: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.4 mg, once weekly, s.c. injection
D: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.8 mg, once weekly, s.c. injection

E: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 0.8 mg with titration, once weekly, s.c. injection
F: Experimental Intervention: Drug: semaglutide	Drug: semaglutide 1.6 mg with titration, once weekly, s.c. injection

Id.

308. NCT00696657 disclosed that the purpose of the study was to identify the efficacy of the treatment to affect HbA1c over the course of 12 weeks:

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.

NCT00696657 at 15.

309. NCT00696657 therefore disclosed the subject matter of the preamble of claim 1.

310. Regarding claim 1's requirement "comprising administering semaglutide," NCT00696657 disclosed that "[s]tudy participants were randomised evenly to treatment with semaglutide." *Id.* at 15. Thus, NCT00696657 disclosed this claim element.

311. NCT00696657 also disclosed the claim element requiring dosing semaglutide "once weekly in an amount of 1.0 mg." NCT00696657 disclosed

that its clinical trial included six experimental arms (arms A-F), in which subjects in the respective arms received once weekly, subcutaneous injections of semaglutide, at doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration). *Id.* at 15-16.

312. Regarding the recited once weekly dose amount of 1.0 mg, a POSA would have immediately envisioned that dose from NCT00696657's description of its experimental arms. A POSA would have noted that NCT00696657's experimental arms included dosing 0.8 mg both with and without titration and dosing 1.6 mg only with titration. NCT00696657 at 15-16. This set of arms would have suggested to a POSA that optimal once weekly dose of semaglutide was somewhere below 1.6 mg and potentially near 0.8 mg, and a POSA would have optimized the once weekly dose within that range to a value of 1.0 mg.

313. Even aside from this, a POSA would have immediately envisioned the 1.0 mg once weekly dose between the tested doses of 0.8 mg and 1.6 mg. A POSA would have understood from the prior art that the use of titration signaled caution regarding whether a particular dose would be tolerable, because titration was described in the prior art as a way to ramp up doses that would be more likely intolerable if given without titration. Here, testing a 1.6 mg dose only with titration signaled potential tolerability problems as a single dose, while testing a 0.8 mg dose both with and without titration signaled the potential for it to be

tolerated as a single dose, and therefore better balancing efficacy and tolerability. This, in turn, would have focused a POSA on an even narrower range where the optimal dose could be found and would have made the 1.0 mg dose even more readily envisioned. Thus, a POSA would have understood that NCT00696657 disclosed the element of claim 1 reciting “once weekly in an amount of 1.0 mg.”²⁰

314. That a POSA would have readily envisioned the 1.0 mg dose is reinforced for at least two additional reasons.

315. First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, a highly similar GLP-1 receptor agonist, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram. *See* Victoza label at 2669 (doses of 0.6 mg, 1.2 mg, and 1.8 mg).

316. Second, for the reasons described above, a POSA would have known that there was an expectation that the effective clinical dose of semaglutide (a 1.0 mg dose administered for the purpose of care and

²⁰ Although I conclude that a POSA would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court’s claim construction requires because it does not require showing a particular degree of efficacy.

management of a patient with Type 2 diabetes) would reside within the disclosed limited range of from 0.8 mg to (at most) 1.6 mg.

317. A POSA would have known from NCT00696657 (as confirmed by NCT00851773)²¹ that semaglutide was tested at doses where the smallest dose step size was 0.1 mg (i.e., stepping up from 0.1 mg to 0.2 mg), and each step of doses occurred in round increments of 0.1 mg. Thus, the range of doses disclosed in NCT00696657 would include, at most, seven options for dosing beyond those already tested, and a POSA would have immediately envisioned all the options in that range at the smallest reasonable step size (i.e., 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, and 1.5 mg).

318. I 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, NCT00696657's disclosure of 0.8 mg to 1.6 mg of

²¹ My citation to the dosing step sizes disclosed by NCT00851773 is confirmatory of the step sizes disclosed by NCT00696657 because the smallest dose step size used in each study was 0.1 mg and steps were designated in even tenths of a milligram. My opinions related to the disclosed step size and the number of dose options a POSA would envision would remain the same without citation to NCT00851773.

semaglutide administered once weekly (in addition to the other tested doses) anticipated the use of 1.0 mg semaglutide administered once weekly as claimed in the '462 patent.

319. Finally, NCT00696657 disclosed claim 1's requirement regarding administering semaglutide "to a subject in need thereof." NCT00696657 disclosed that it was an "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." NCT00696657 at 15. A POSA would have known that treating a patient having type 2 diabetes was inherently giving semaglutide "to a subject in need thereof."

320. Thus, in my opinion, for at least the above reasons, NCT00696657 disclosed all elements of claim 1 of the '462 patent and therefore anticipated it.

b. NCT00696657 anticipated claim 3

321. Regarding the requirement of claim 2 that "semaglutide is administered by parenteral administration" and the requirement of claim 3 that the parenteral administration occurs "by subcutaneous injection," NCT00696657 disclosed that semaglutide was administered "once weekly, s.c. injection." NCT00696657 at 15-16. A POSA would have understood "s.c. injection" to refer to subcutaneous injection, and would have understood that subcutaneous injection is a type of parenteral administration.

322. Thus, in my opinion, NCT00696657 disclosed the subject matter of claims 2 and 3 for all the same reasons described above and with respect to claim 1 and therefore anticipated claim 3.

3. *Lovshin*²²

a. Lovshin anticipated claim 1

323. 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.” In my opinion, Lovshin taught each and every element of claim 1 of the '462 patent and therefore anticipated it.

324. Lovshin disclosed a “method for treating type 2 diabetes, comprising administering semaglutide.” Lovshin disclosed investigation of the treatment of type 2 diabetes with the agent NN9535 by subcutaneous injection. Lovshin at 263 (Table 1: “GLP-1R agonists [by] (subcutaneous injection)” including “NN9535 0.1–1.6 mg once weekly”).

325. NN9535 is and was known to be semaglutide. *See* NCT00696657 at 3 (NN9535 is semaglutide); Bhansali at 13 (“Semaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes.”); Novo Pipeline at 1 (“Semaglutide (NN9535)

²² The content of Lovshin is also described above. *See* Section VIII.A.

is a once weekly human GLP-1 analogue, which is being developed by Novo Nordisk for the treatment of type 2 diabetes. Semaglutide lowers blood glucose through stimulating release of insulin, and additionally lowers body weight.”).

326. Lovshin noted that “incretins exert antidiabetic actions in a glucose-dependent manner,” and that NN9535 (semaglutide) is an “incretin-based therapy.” *Id.* at 263, Table 1; *see also id.* (“Key points”: “Glucagon-like peptide 1 receptor (GLP-1R) agonists, but not dipeptidyl peptidase-4 (DPP-4) inhibitors, inhibit gastric emptying and might cause weight loss.”). Lovshin further disclosed that NN9535 (semaglutide) is a GLP-1 receptor agonist (like liraglutide and exenatide), *id.* at 263 (Table 1), and that “[c]ontinuous, subcutaneous administration of native GLP-1 to patients with type 2 diabetes mellitus (T2DM) lowers fasting and postprandial levels of glucose and HbA_{1c} effectively, and also results in weight loss,” *id.* at 262.

327. A POSA would have understood from these disclosures (e.g., from the language “exert antidiabetic actions”) that Lovshin disclosed a method “for the purpose of care and management of a patient with Type 2 diabetes” or “intended to care for and manage a patient with Type 2 diabetes,” and that such method would be used with a patient in need of such treatment. This is a disclosure of the subject matter of the preamble of claim 1, which the Court ruled

was limiting but did not require a particular degree of efficacy. *See* Section VI above.

328. With respect to the claim element “comprising administering semaglutide,” Lovshin disclosed that semaglutide was “under active clinical investigation in phase I–II studies,” *id.* at 266, and a POSA would have known that phase I and II clinical studies involve administering treatments to patients. Lovshin also disclosed that liraglutide was administered once daily to patients with type 2 diabetes and was well tolerated and effectively reduced HbA_{1c} levels without hypoglycemia. *Id.* at 264. Further, Lovshin disclosed that “[a] 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg or 1.8 mg daily) in patients with T2DM. Liraglutide was more effective than glimepiride for reducing HbA_{1c} level (by 0.84% and 1.14% versus 0.5%, respectively). Moreover, patients treated with liraglutide lost weight and exhibited a reduction in blood pressure, whereas those treated with glimepiride gained weight.” *Id.* In addition, Lovshin 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 263. For at least these reasons, a POSA would have understood that semaglutide, like liraglutide, exenatide, and other GLP-1 receptor agonists, was administered to patients.

329. Lovshin disclosed a dosage of “0.1–1.6 mg once weekly” semaglutide for treating type 2 diabetes mellitus, given by “subcutaneous injection.” Lovshin at 263 (Table 1). A POSA 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 discrete dosing steps proceeding in increments of no less than 0.1 mg, including a step at 1.0 mg.

330. First, a POSA would have known that, earlier than the priority date, liraglutide had been approved as Victoza, a highly similar GLP-1 receptor agonist, and that the doses of Victoza were broken down to increments of no less than a tenth of a milligram. *See* Victoza label at 2669 (doses of 0.6 mg, 1.2 mg, and 1.8 mg).

331. 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. Lovshin at 263 (Table 1), 266. From this, a POSA would have known that there was an expectation that the effective clinical dose of semaglutide would reside within this disclosed limited range. At

minimum, a POSA would have expected that the effective clinical dose of semaglutide would reside within this disclosed limited range, and that a 1.0 mg dose could be administered for the purpose of care and management of a patient with Type 2 diabetes with a reasonable expectation of success.

332. Known prior art clinical trials testing once weekly subcutaneous administration of semaglutide would have confirmed this conclusion and expectation. *See, e.g.*, NCT00696657 at 15-16, NCT00851773 at 7. A POSA would have known that in NCT00696657, semaglutide was tested at doses of 0.1, 0.2, 0.4, and 0.8 mg, and doses leading up to 0.8 mg (“0.8 mg with titration”) and 1.6 mg (“1.6 mg with titration”), NCT00696657 at 15-16, and that in NCT00851773,²³ semaglutide was tested at doses of 0.1, 0.2, and 0.4 mg, 0.8 mg with titration, and 1.2 mg with titration. NCT00851773 at 7. Thus, the smallest dose step size used in NCT00696657 and NCT00851773 was 0.1 mg, and the

²³ My citation to the dosing step sizes disclosed by NCT00851773 is confirmatory of the step sizes disclosed by NCT00696657 because the smallest dose step size used in each study was 0.1 mg and steps were designated in even tenths of a milligram. My opinions related to the disclosed step size and the number of dose options a POSA would envision would remain the same without citation to NCT00851773.

range of doses disclosed in Lovshin would include, at most, 16 options for dosing and a POSA would have immediately envisioned all the options in that range at the smallest reasonable step size (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).

333. I 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 0.1 mg to 1.6 mg of semaglutide administered weekly anticipated the use of 1.0 mg semaglutide administered once weekly claimed in the '462 patent.

334. Finally, on dosing, a POSA would have immediately envisioned in Lovshin a dose of 1.0 mg semaglutide administered once weekly for use in the claimed method of treatment. That is because a POSA would have understood that doses within the disclosed range of 0.1-1.6 mg were likely to be effective, particularly doses at the upper end of the range. *See* NCT00696657 (as of the priority date, semaglutide had been the subject of a clinical study with dose ranges going from 0.1 mg up to, at most, 1.6 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was below 1.6 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg), NCT00851773 (as of the priority date, semaglutide had been the subject of another clinical study with dose ranges going from 0.1 mg up to, at most, 1.2 mg

or 1.6 mg once weekly, suggesting to a POSA that the focus for semaglutide dosing was below 1.2 mg or 1.6 mg, dosed once weekly, and a POSA would have optimized the dose in that range to 1.0 mg).²⁴

335. Regarding treating “a subject in need thereof,” Lovshin also disclosed that incretins/GLP-1 receptor agonists like semaglutide are used in a method of treating type 2 diabetes. Lovshin is entitled, “*Incretin-based therapies for type 2 diabetes mellitus.*” Lovshin at 262. Lovshin further disclosed that exenatide, the “first GLP-1 [receptor] agonist to be approved for human clinical use,” was used as a treatment in patients with type 2 diabetes. Lovshin at 263.²⁵ 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 264. Further, Lovshin disclosed that “[a] 52-week study compared glimepiride monotherapy with liraglutide monotherapy (1.2 mg

²⁴ Although I conclude in this discussion that a POSA would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court’s claim construction requires because it does not require showing a particular degree of efficacy.

²⁵ The discovery and development of exenatide was a game changing advance in diabetes treatment.

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

336. Thus, in my opinion, for at least the above reasons, Lovshin disclosed all elements of claim 1 of the ’462 patent and therefore anticipated it.

b. Lovshin anticipated claim 3

337. Regarding the requirement of claim 2 that “semaglutide is administered by parenteral administration” and the requirement of claim 3 that the parenteral administration occurs “by subcutaneous injection,” Lovshin disclosed that NN9535 (semaglutide) is administered by “subcutaneous injection.” Lovshin at 263 (Table 1). As of the priority date of the ’462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous, intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump, Knudsen patent at 170:25-29, and therefore would have understood that the “subcutaneous injection” Lovshin disclosed is a type of parenteral administration of a solution.

338. Thus, in my opinion, Lovshin disclosed the subject matter of claims 2 and 3 for all the same reasons described above and with respect to claim 1 and therefore anticipated claim 3.

* * *

339. Thus, WO '421, NCT00696657, and Lovshin each explicitly or inherently disclosed the methods for treating type 2 diabetes recited in claims 1 and 3 of the '462 patent.

340. For at least these reasons, it is my opinion that claims 1 and 3 of the '462 patent are invalid as anticipated.

B. All Asserted Claims of the '462 Patent Would Have Been Obvious Over the Prior Art

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

342. In my opinion, the prior art, taken as a whole, disclosed, taught, and/or suggested each and every element recited in the claims of the '462 patent. In addition, there was motivation to modify the prior art to arrive at the claimed inventions of the '462 patent, and to do so with a reasonable expectation of success.

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

- a. Claims 1 and 3

343. Claim 1 reads:

1. A method for treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof.

'462 patent at 35:42-44.

344. The Court held that claim 1's preamble, "[a] method for treating type 2 diabetes," means that "the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes" or "the claimed administration is intended to care for and manage a patient with Type 2 diabetes." D.I. 148 at 2-3. I understand that the Court made clear that its construction does not require a particular degree of efficacy for the claimed method.

345. Claim 2 depends from claim 1 and adds the limitation "wherein the semaglutide is administered by parenteral administration;" claim 3 depends from claim 2 and adds the limitation "wherein the solution is administered by subcutaneous injection."²⁶ *Id.* at 35:45-48. As of the relevant priority date, it was

²⁶ Claim 3 actually recites, "[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection."

well known that GLP-1 analogues such as semaglutide could be therapeutically useful for treating type 2 diabetes, and determining the dosing conditions recited in claims 1 and 3 of the '462 patent would have been obvious to a POSA, in my opinion.

346. WO '421 disclosed “[m]ethods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO '421 at 1:4-7. NCT00696657 disclosed a Phase 2 interventional trial entitled “Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or Controlled With Diet and Exercise[.]” NCT00696657 at 15. Under “Condition,” NCT00696657 identified “Diabetes Mellitus, Type 2.” *Id.* Lovshin disclosed that “[i]ncretin-based drugs, such as glucagon-like peptide-1 receptor agonists and dipeptidyl peptidase 4 inhibitors, are now routinely used to treat type 2 diabetes mellitus.” Lovshin at 262.

'462 patent at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

347. WO '537²⁷ disclosed “[a]n embodiment provides the use of a [GLP-1] compound according to any one of the embodiments . . . for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” WO '537 at 22:24–23:3. WO '537 further disclosed, “[i]n one embodiment a compound according to the invention is used for the preparation of a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, obesity” WO '537 at 37:34-36.

348. WO '421 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,” each of which was disclosed to have “significant sequence identity to GLP-1.” WO '421 at 33:20-26 (emphasis added). NCT00696657 further disclosed that trial “participants were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or liraglutide (1.2 mg QD,

²⁷ WO '537 shares a specification with U.S. Patent Application Publication No. 2009/0156478 and U.S. Patent No. 8,129,343. Citations to WO '537 therefore refer equally to citations to the same content in those related documents.

or 1.8 mg QD).” NCT00696657 at 15; *see also* WO ’421 at 43:7-19 (disclosing overlapping dosage amounts for several GLP-1 receptor agonists, including liraglutide and semaglutide). Lovshin disclosed investigation of the treatment of type 2 diabetes with the agent NN9535 by subcutaneous injection. Lovshin at 263 (Table 1). NN9535 is and was known to be semaglutide. *See* NCT00696657 (NN9535 is semaglutide).²⁸

²⁸ *See also* WO ’193 at 34:18 (“semaglutide/NN9535 (Novo Nordisk)”); Bhansali at 13 (“[s]emaglutide (NN9535) is a once-weekly human GLP-1 analogue that is being developed by Novo Nordisk for the treatment of type 2 diabetes”); Novo Pipeline at 1 (“Semaglutide (NN9535) is a once weekly human GLP-1 analogue, which is being developed by Novo Nordisk for the treatment of type 2 diabetes.”); ’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.”); WO ’537 at 47:4-22 (Example 4); ’462 patent at 9:43-45 (admitting that WO ’537 at 47:4-22 (Example 4) discloses the semaglutide sequence and that it is “a mono-acylated GLP-1 agonist for once weekly administration”).

Example 4

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

The chemical structure represents a complex peptide derivative. It features a long heptadecanoyl chain (17:0) attached to a butyryl chain (4:0) via an amide bond. This is followed by a series of ethoxy linkers and acetyl groups, ending with a carboxylic acid group. The peptide backbone is shown with side chains for Aib8 and Arg34, and the GLP-1-(7-37) peptide sequence.

350. WO '537 disclosed once weekly administration of GLP-1 peptides, including semaglutide. “One aspect of this invention is to prepare GLP-1 analogues/derivatives with extended plasma half-lives that are suitable for once weekly administration.” WO '537 at 59:24-25.

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

WO '537 at 59:28-32.

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

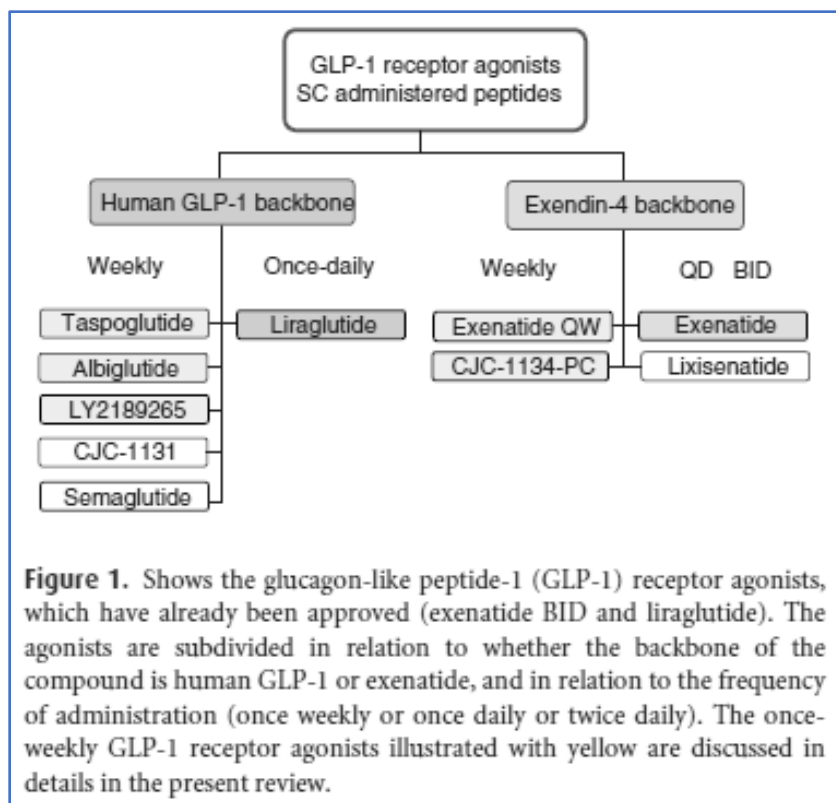
352. The '833 patent similarly disclosed:

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

'833 patent at 13:45-50.

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

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



Id. at 395.

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

356. WO '421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” WO '421 at 43:13. NCT00696657 disclosed that trial “participants were randomised evenly to treatment with semaglutide (0.1 mg QW – 1.6 mg QW[]), 6 treatment arms, placebo or

liraglutide (1.2 mg QD, or 1.8 mg QD).” NCT00696657 at 15. The NCT00696657 trial included treatment with semaglutide at six different semaglutide doses or dosing regimens, including 0.8 mg (with and without titration) and 1.6 mg with titration, and once weekly by subcutaneous injection. *See id.* at 16.

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

357. Lovshin disclosed treatment at a dose of 0.1 mg to 1.6 mg semaglutide once per week. Lovshin at 263 (Table 1). WO ’537 further disclosed that formulations can be prepared at a variety of different concentrations, such as from 0.1 mg/mL to 25 mg/mL. WO ’537 at 24:11-13.

358. Thus, WO ’421, NCT00696657, WO ’537, and Lovshin each 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.”

359. A POSA would have understood these to be disclosures of ranges of semaglutide doses including 1.0 mg once weekly. Alternatively, the dosage range disclosed by WO '421, NCT00696657, and Lovshin, and the use of WO '537 in a once weekly regimen, rendered the claimed 1.0 mg dosage obvious.

360. By routine testing of this range of dosages, which encompassed the claimed 1.0 mg once weekly dose, a POSA would have been motivated with a reasonable expectation of success to use a weekly dose of 1.0 mg semaglutide by subcutaneous injection to treat type 2 diabetes. A POSA's routine optimization of this range would have yielded an effective dose of semaglutide that minimizes known side effects (i.e., an optimal dose), such as those known to be caused by compounds in the GLP-1 receptor agonist class, like semaglutide. The motivation to use once weekly semaglutide would have come at least from the benefit of reduced frequency of injections and improved patient compliance. *See, e.g.,* Lund at 611 (“The once-weekly regime is thought to improve compliance, and to offer an improved throughout-the-day glycemic control compared with the currently available GLP-1R agonists (exenatide and liraglutide).”). A POSA would have a reasonable expectation of success practicing the claimed “method for treating type 2 diabetes” with a once weekly 1.0 mg dose of semaglutide because a POSA would have expected the 1.0 mg dose to have some efficacy,

just like liraglutide before it,²⁹ and the Court's construction, as I understand, does not require a particular degree of efficacy.

361. Indeed, the '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious to a POSA:

[A]n "effective amount" of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as "effective amount". Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary [sic].*

'462 patent at 5:4-15 (emphasis added).

362. The ability of a POSA to determine an optimal dosage from a range is reinforced by the '833 patent, which disclosed:

[I]t is understood that depending on the peptide or peptides included in the formulations of the invention, the formulations may be used

²⁹ Seino at 166 ("A clear dose response relationship for HbA1c reduction was shown in this study. All doses of liraglutide tested showed a degree of efficacy").

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

'833 patent at 13:60–14:15 (emphasis added).

363. Identifying the 1.0 mg dose of semaglutide once weekly as an effective dose³⁰ in a method for treating type 2 diabetes would have been obvious, as well, in view of the prior art.

364. At least as of the '462 patent's 2012 priority date, a POSA would have known of the once weekly doses of semaglutide doses tested in NCT00696657, as described throughout this report; namely: 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. *See* NCT00696657

³⁰ Although I conclude that a POSA would have understood a 1.0 mg dose of semaglutide to be effective, this goes further than the Court's claim construction requires because it does not require showing a particular degree of efficacy.

at 15-16. A POSA also would have known that NCT00696657 tested the 0.8 mg dose both with and without titration, but the 1.6 mg dose was tested only with titration. *See* NCT00696657 at 15-16. Because a POSA would have known of the risk of side effects with higher doses of GLP-1 receptor agonists, and would have known that titration was a way to deal with such side effects, the requirement for titration with the 1.6 mg dose, and testing of the 0.8 mg dose both with and without titration, would have suggested to a POSA that the 1.6 mg dose was likely beyond the optimal dose, while 0.8 mg was more likely near it. A POSA would therefore have been motivated to optimize the dose to 1.0 mg within the range from 0.8 to 1.6 mg.

365. In addition, NCT00851773 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. NCT00851773 at 7-8.³¹ NCT00851773 reported that the clinical trial started in February 2009 and was

³¹ My analysis of what NCT00851773 taught a POSA is not essential to my opinion that claims 1, 3, 4, 5, and 7 would have been obvious over WO '421, NCT00696657, WO '537, and/or Lovshin. NCT00851773's teachings just confirm the obviousness of claims 1, 3, 4, 5, and 7 over WO '421, NCT00696657, WO '537, and/or Lovshin.

completed in October 2009. NCT00851773 at 7. A POSA would have known from NCT00696657, and a variety of other prior art cited here, that semaglutide could be used to treat type 2 diabetes.

366. In one of the NCT00851773 experimental arms, semaglutide was administered with titration 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.” NCT00851773 at 7. The trial included five different semaglutide dosing regimens, including 0.8 mg and 1.2 mg final dose amounts, and all were injected once weekly, subcutaneously (“s.c.”):

▼ 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

NCT00851773 at 7.

367. A POSA would have recognized that the proposed and used doses in NCT00851773 changed over time. First, a POSA would have known that NCT00851773 was originally planned to investigate a dose range of 0.1-1.6 mg

semaglutide once weekly, with the 1.6 mg dose required to be tested with titration, in both cases like NCT00696657. *See* NCT00851773 at 11 (August 26, 2009 update). This same plan showed that the 0.8 mg dose would be tested both with and without titration, again like NCT00696657. *Id.* But NCT00851773 also included a dose step not included in NCT00696657: a “[d]ose to be determined based on safety and tolerability of previous dose steps,” titrated up from 0.4 mg and 0.8 mg, that “will only be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.” NCT00851773 at 11 (August 26, 2009 update). This dosing plan would have confirmed to a POSA that the optimal dose of once weekly semaglutide was somewhere between 0.8 mg and 1.6 mg, and would have motivated a POSA to optimize the dose to 1.0 mg, because here and in NCT00696657 the 0.8 mg dose was being tested both with and without titration, the 1.6 mg dose required titration, and an optional dose was contemplated as following a dose titration scheme from a 0.4 mg dose to a 0.8 mg dose to a “to be determined” dose. The “to be determined” dose would naturally have been beyond 0.8 mg (because it was a step in the titration) but below 1.6 mg (because it was already being tested).

368. Second, a POSA would have known, as discussed elsewhere, that the next update to the NCT00851773 protocol eliminated the 1.6 mg dose and the “to be determined” dose became 1.2 mg, tested only with titration. *See*

NCT00851773 at 15 (July 15, 2010 update). This would have confirmed to a POSA that the optimal dose of once weekly semaglutide was somewhere between 0.8 mg and 1.2 mg, and would have motivated a POSA to optimize the dose to 1.0 mg.

369. A POSA would have known generally from the prior art, in addition to the teachings of NCT00696657 and NCT00851773, that semaglutide was being investigated by Novo Nordisk 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* Lovshin at 263 (Table 1), 5; *see also* Lund at 613-14 (“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).”), 609 (Fig. 1) (semaglutide is a once weekly GLP-1-based treatment), 610 (Table 1) (semaglutide is a once weekly formulation in Phase II development); ’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.”); 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); WO ’421 at 43:31 (“Semaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).”); Novo Pipeline at 1-3.

370. 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 NCT00696657 and NCT00851773 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* Tamimi at c128 (“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.”).

371. Additionally, a POSA would have known from the prior art and, especially, from WO '421, Lovshin, and NCT00696657 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 NCT00696657 were 0.1 mg, 0.2 mg, 0.4 mg, 0.8 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* Tamimi at c127-28 (“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.*, Knudsen 2010b (describing the significant preclinical work involving liraglutide, including in mouse, rat, and minipig animal models).

372. A POSA would have recognized from NCT00851773 that a) it followed directly in time from NCT00696657, and b) it narrowed the range of

semaglutide doses being tested. In the table below are shown the reported start and end dates of the NCT00696657 Phase II and NCT00851773 Phase I clinical trials, and the semaglutide doses used in each of NCT657 and NCT773:

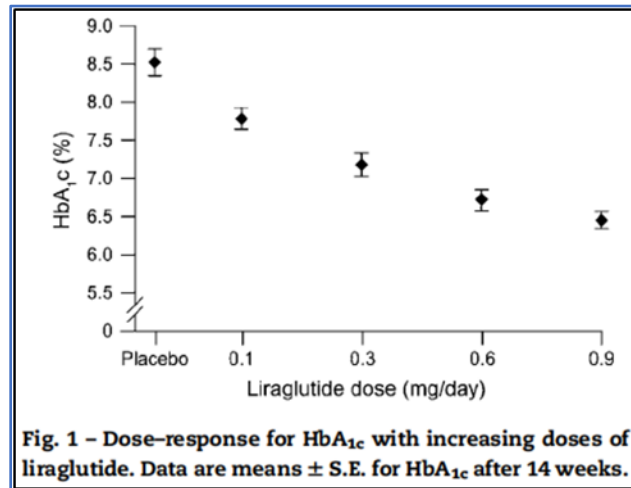
NCT657 doses (start 6/2008; end 2/2009)	NCT773 doses (start 2/2009; end 10/2009)
0.1 mg	0.1 mg
0.2 mg	0.2 mg
0.4 mg	0.4 mg
0.8 mg	[not tested]
0.8 mg titrated	0.4, then 0.8 mg
1.6 mg titrated	0.4, then 0.8, then 1.2 mg

NCT00696657 at 15-16; NCT00851773 at 7.³²

373. 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). *Compare* NCT00696657 at 15 *with* NCT00851773 at 7. A POSA would have concluded from this 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.*, Seino at 164 (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

³² NCT00851773 disclosed that the study was performed in “Japanese and Caucasian subjects,” but the claims of the ’462 patent are not limited similarly.

by decrease in HbA_{1c}; a POSA would have expected semaglutide to have a curve of similar shape given its close relation to liraglutide):



374. A POSA would have recognized that the nontitrated 0.8 mg dose tested in NCT00696657, NCT00696657 at 15-16, was eliminated in NCT00851773, in favor of testing again the “titrated” 0.8 mg dose (0.8 mg reached with an initial step of 0.4 mg), NCT00851773 at 7.

375. A POSA also would have recognized that the highest doses tested in NCT00851773 differed from, and were lower than, the highest doses tested in NCT00696657. In short, the NCT00851773 study eliminated the titrated 1.6 mg (highest) dose used in NCT00696657 and replaced it with a titrated 1.2 mg dose. NCT00851773 at 7. This would have led a POSA to conclude that doses lower than 1.6 mg (in fact, 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.

376. Finally, a POSA would have noted that the two highest doses tested in NCT00851773 (i.e., 0.8 mg and 1.2 mg, 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 optimal target dose.

377. 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, narrowing even further the ranges disclosed in prior art like WO '421, NCT00696657, and Lovshin, 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).

378. In my opinion, a POSA therefore 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. *See, e.g.,* Seino at 166 (“A clear dose response relationship for

HbA1c reduction was shown in this study [of liraglutide]. All doses of liraglutide tested showed a degree of efficacy”).³³

³³ As noted elsewhere, the prior art discussed here and above would have motivated a POSA to use a 1.0 mg dose of semaglutide once weekly, with a reasonable expectation of success that it would be effective to treat type 2 diabetes. I understand that the Court determined that the preamble of claim 1, “[a] method for treating type 2 diabetes,” means that “the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with Type 2 diabetes.” D.I. 148 at 2-3. I also understand that the Court construed that term so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2 diabetes as the Court has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Court’s interpretation requires in terms of efficacy. That is, I believe the prior art would motivate a POSA to use a once-weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide significantly more than a minimal level of efficacy in treating type 2 diabetes.

379. As described earlier, a POSA would have known from the prior art that liraglutide and semaglutide shared substantially the same amino acid backbone (i.e., the portion of the molecule that renders it effective to bind the GLP receptor), and the residues important for binding to the GLP-1 receptor, and therefore would have reasonably expected them to behave in similar fashion as GLP-1 receptor agonists. *See, e.g.*, Sections VII.D, VIII.G.6; Knudsen 2004, Fig. 3 (identifying residues “essential for binding” and “[u]nique for GLP-1,” all of which are found in semaglutide); Lund at 610, Table 2 (showing sequence homology for GLP-1 and several GLP-1 receptor agonists and the broad conservation of residues identified by Knudsen 2004). 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* Lovshin at 263-66 (identifying, in addition to liraglutide: exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC1134, LY2199265, and LY2428757, several of which were once weekly formulations); *see also* 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 way generally consistent with these GLP-1 receptor agonists, given the similarity in structure and pharmacology among the several compounds. *See* Knudsen 2004 at 4130, Fig. 3 (showing important conserved GLP-1 residues); *id.*, Figs. 1 and 2 (GLP-1 and liraglutide sequences); '462 patent at 9:43-44 (admitting that WO '537 at 48:4-22 (Example 4) disclosed the semaglutide sequence and its use once weekly); 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).

380. A POSA's knowledge related to dosing in NCT00696657 and NCT00851773, which confirmed NCT00696657's teachings, as detailed above (*see, e.g.*, paragraphs 372-377), would have added to the POSA's reasonable expectation of success given the POSA's knowledge related to clinical trial design, the clinical trial teachings, and the prior art detailed above. 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.

381. In addition to these teachings about the claimed dosing regimen, a POSA would have known how to formulate use a semaglutide solution as a

subcutaneous injection, a type of parenteral administration. For example, WO '421 disclosed:

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

Id. at 39:23-26; *see also* NCT00696657 at 15-16 (describing subcutaneous injection), Lovshin at 263 (same), WO '537 at 34:3-4, 15-16 (same). Moreover, a POSA would have been aware of knowledge in the art regarding subcutaneous pharmaceutical formulations. *See, e.g.*, WO '537 at 63:10-15 (disclosing an exemplary semaglutide formulation with a concentration of 6.25 mg/ml semaglutide); *id.* at 5:32-35 (disclosing pharmaceutical formulations comprising GLP-1 compounds, such as semaglutide, along with excipients).

382. WO '537 disclosed that “[c]ompositions of the current invention are specifically useful in formulation of controlled, sustained, protracting, retarded and slow release drug delivery systems. More specifically, but not limited to, compositions are useful in formulation of parenteral controlled release and sustained release systems.” WO '537 at 33:35–34:2.

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

384. A POSA viewing the teachings of WO '421, NCT00696657, WO '537, and/or Lovshin, optionally in view of one or more of the '833 Patent, and Madsbad, in light of the POSA's knowledge would have been motivated with a reasonable expectation of success to utilize parenteral administration of 1.0 mg semaglutide by subcutaneous injection once weekly for the treatment of type 2 diabetes. Claims 1 and 3 of the '462 patent thus claim a known compound (semaglutide) for a known purpose (treating type 2 diabetes) at a dose that falls within the prior art-disclosed range, administered by a known technique. This would have been obvious to a POSA.

385. For at least these reasons, it is my opinion that claims 1 and 3 of the '462 patent are invalid under 35 U.S.C. § 103 because they would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin, optionally in view of one or more of the '833 Patent and Madsbad, in view of the knowledge of a person of ordinary skill in the art.

b. Claim 4, 5, and 7

386. It is my opinion that claims 1 and 3 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin in combination with the '833 Patent, optionally in view of Madsbad, in view of the knowledge of a person of ordinary skill in the art, 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 and 3 of the '462 patent. However, I understand it is Dr. Dalby's opinion that the asserted art disclosed all formulation-related elements of claims 4, 5, and 7 of the '462 patent.

387. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin in combination with the '833 Patent, optionally in view of Madsbad, in view of the knowledge of a person of ordinary skill in the art for the reasons addressed in Section IX.B.1.a and by Dr. Dalby.

* * *

388. It is therefore my opinion that claims 1, 3, 4, 5, and 7 of the '462 patent are invalid because they would have been obvious over WO '421, NCT00696657, WO '537 and/or Lovshin, optionally in view of one or more of the '833 Patent and Madsbad.

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

a. Claim 1

389. 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.” In my opinion, claim 1 of the '462 patent would have been obvious to a POSA over WO '421 alone or in view of the '833 patent.

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

390. The disclosures of WO '421 are described above.

391. WO '421 disclosed “methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor.” WO '421 at 1:4-7. WO '421 further disclosed that “[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide.” *Id.* at 33:20-22 (emphasis added).

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

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

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

diabetes patients particularly in the type 2 diabetes segment are subject to so-called ‘needle-phobia’, i.e. a substantial fear of injecting themselves. In the type 2 diabetes segment most patients are treated with oral hypoglycaemic agents, and since GLP-1 compounds are expected to be the first injectable product these patients will be administered, the fear of injections may become a serious obstacle for the widespread use of the clinically very promising GLP-1 compounds. Thus, there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile.”); Jimenez-Solem at 794 (“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.”). Given that semaglutide was already in the prior art, it would have been obvious to a POSA to further optimize the dose of semaglutide for the treatment of type 2 diabetes. Moreover, as detailed below, a significant amount of information was already in the prior art directing a POSA to the right dose.

395. First, a POSA would have been generally motivated to optimize the prior art dosing range of semaglutide by a desire to select the optimal treatment dose, yielding a treatment with the best benefits for patients while providing

minimal side effects, which is consistent with general principles of dose selection and drug optimization (moving upward to the greatest treatment effect without incurring dose-limiting toxicities or side effects, such as nausea and vomiting).

396. As described above, a POSA would have understood that WO '421's disclosure of a dosing range from 0.1-1.6 mg for semaglutide was ultimately the disclosure of, at most, 16 possible dosing choices. However, even within the range of 16 possible doses, a POSA would have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of WO '421's disclosed range, as also described here. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), which has substantially the same amino acid backbone as semaglutide, was approved in January 2010 in doses of 0.6, 1.2, and 1.8 mg. *See* Victoza label. A POSA would also have known from the Victoza label (*see, e.g.*, label approved January 2010) that Victoza's 1.2 mg dose was the targeted dose for long-term therapy, with the 1.8 mg dose used only "[i]f the 1.2 mg dose does not result in acceptable glycemic control." *Id.* at 2669. 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 (with and without titration), and doses leading up to 1.6 mg ("1.6 mg with titration"), *see* NCT00696657 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* NCT00851773 at 7.³⁴

397. Further, from one or more of these disclosures in the prior art (e.g., from WO '421, NCT00696657, and/or NCT00851773), a POSA would have expected that, by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to use in that method, the doses disclosed in the prior art would function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work for treating type 2 diabetes. And, the '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious:

[A]n “effective amount” of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as “effective

³⁴ My citation to the dosing range disclosed by NCT00851773 is confirmatory of the dosing range disclosed by NCT00696657 because each bracketed the ultimate optimal treatment dose that would have been obvious to a POSA. My opinions related to the disclosed dose range within which the obvious dose would have been found by a POSA would remain the same without citation to NCT00851773.

amount”. Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary [sic].*

’462 patent at 5:4-15 (emphasis added).

398. Additionally, a POSA would have been motivated to try the 1.0 mg dose in the dose range disclosed by WO ’421. A POSA would have known from WO ’421 that the range of potential doses of semaglutide was 0.1-1.6 mg. WO ’421 at 35:23-36:5, 43:13. And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options to try for administration to patients for the treatment of type 2 diabetes, as described above in detail. *See, e.g.,* Sections IX.A.1.a, IX.A.3.a.

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

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

400. 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 have substantially 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. *See* Knudsen 2004, Fig. 3 (identifying residues “essential for binding” and “[u]nique for GLP-1,” all of which are found in semaglutide); Lund at 610, Table 2 (showing sequence homology for GLP-1 and several GLP-1 receptor agonists and the broad conservation of residues identified by Knudsen 2004). A POSA also would have known that liraglutide and semaglutide shared amino acids known from earlier work and available in the prior art, Knudsen 2004 at 4130, 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

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

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

401. A POSA also would have known that there were several other GLP-1-related compounds being studied in both human and preclinical trials, each of which was known to be effective to reduce one or more of HbA_{1c} levels, body weight, and blood glucose concentrations, while avoiding the complication of hypoglycemia. *See, e.g.*, Lovshin at 263-66 (identifying, in addition to liraglutide: exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC1134, LY2199265, and LY2428757, several of which were once weekly formulations) *see also* 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 way generally consistent with these GLP-1 receptor agonists, given the similarity in structure and pharmacology among the several compounds. *See, e.g.*, Knudsen 2004 at 4130, Fig. 3 (showing conserved important GLP-1 residues); *id.* Figs. 1

and 2 (GLP-1 and liraglutide sequences); '462 patent at 9:43-45 (admitting that WO '537 at 47:4-22 (Example 4) discloses the semaglutide sequence and that it is “a mono-acylated GLP-1 agonist for once weekly administration”); Knudsen 2004 at 4130, Figure 3 (showing conservation in liraglutide and semaglutide of residues known to be essential for binding); 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).

402. On a related note, a POSA also would have known that semaglutide had been tested in clinical trials, with once weekly subcutaneous administration at doses of 0.1, 0.2, 0.4, 0.8 mg (with and without titration), and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657 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* NCT000851773 at 7.³⁵ While the

³⁵ My citation to the dosing range disclosed by NCT00851773 is confirmatory of the dosing range disclosed by NCT00696657 because each bracketed the ultimate optimal treatment dose that would have been obvious to a POSA. My opinions related to the disclosed dose range within which the obvious dose would have been found by a POSA would remain the same without citation to NCT00851773.

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, and the trials were complete (*see, e.g.*, Novo Pipeline at 1-3, Bhansali at 13), 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.*, Knudsen 2010b (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.*, Seino at 164 (dose-response curve for HbA1c response versus liraglutide dose, showing suboptimal effects for the lower doses). A POSA reading WO '421 would have this background knowledge.

403. A POSA therefore would have optimized the known weekly dosing range for semaglutide, 0.1 mg to 1.6 mg. And separately and relatedly, would have had a reasonable expectation of success treating type 2 diabetes with a 1.0 mg weekly dose of semaglutide. *See also, e.g.*, Seino at 166 ("A clear dose response relationship for HbA1c reduction was shown in this study [of

liraglutide]. All doses of liraglutide tested showed a degree of efficacy”). Thus, in my opinion, claim 1 of the ’462 patent would have been obvious to a POSA in view of WO ’421.

b. Claim 3

404. Claim 2 of the ’462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.” Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”³⁶

405. WO ’421’s specification disclosed the subject matter of claim 2 for all the same reasons described with respect to claim 1, and further because WO ’421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. WO ’421 at 35:23-36:5, 43:13.

406. As of the priority date of the ’462 patent, a POSA would have known that “[p]arenteral administration may be performed by subcutaneous,

³⁶ Claim 3 actually recites, “[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection.” ’462 patent at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

intramuscular or intravenous injection by means of a syringe, optionally a pen-like syringe,” or by means of an infusion pump. Knudsen patent at 170:25-29; *see also* WO ’421 at 64:27-31 (claim 17 reciting “[a] *GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin,*” which the specification instructs would have been accomplished by “subcutaneous injection” (WO ’421 at 35:23-36:5, 43:13) (emphasis added)). Therefore, a POSA would have understood that the “subcutaneous injection” disclosed in WO ’421 is a type of parenteral administration.

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

408. WO ’421 disclosed the subject matter of claim 3 for all the same reasons described with respect to claims 1 and 2, and further because WO ’421 disclosed that “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)” to treat type 2 diabetes. WO ’421 at 35:23-36:5, 43:13; *see also* WO ’421 at 64:27-31 (claim 17 reciting “[a] *GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide,*

albiglutide, lixisenatide and dulaglutide, *for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin,*” which the specification instructs would have been accomplished by “subcutaneous injection” (emphasis added)).

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

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

c. Claims 4, 5, and 7

411. It is my opinion that claims 1 and 3 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent, 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 and 3 of the '462 patent. However, I understand it is Dr. Dalby's opinion that the asserted art disclosed all formulation-related elements of claims 4, 5, and 7 of the '462 patent.

412. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious over WO '421 alone or in view of the '833 patent for the reasons addressed in Section IX.B.2.a and b and by Dr. Dalby.

* * *

413. It is therefore my opinion that claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious to a POSA over WO '421 alone or in view of the '833 patent.

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

a. Claim 1

414. 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.”

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

415. The disclosures of WO '537 are also described above.

416. WO '537 disclosed using modified GLP-1 peptides to treat type 2 diabetes, i.e., that the composition “may be administered to a patient in need of such treatment.” WO '537 at 23:24-29, 33:32-33. Example 4 of WO '537 discussed semaglutide, *id.* at 48:4-22, and a patient with type 2 diabetes in need of treatment with a GLP-1 peptide, which improves glycemic control, *id.* at 23:24-26; *see also* '462 patent at 9:43-45 (admitting that WO '537 at 47:4-22 (Example 4) discloses the semaglutide sequence and that it is “a mono-acylated GLP-1 agonist for once weekly administration”).

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

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

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

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

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

420. Lovshin disclosed, further, that NN9535 (i.e., semaglutide, as a POSA would have been known)³⁷ was being investigated for once weekly dosing in the 0.1-1.6 mg dose range. Lovshin at 263, Table 1. It would have been obvious to a POSA to optimize the dose of semaglutide to a dose of 1.0 mg and/or the 1.0 mg dose would have been obvious to try in that disclosed dose range, and the POSA would have been motivated to do so by a desire to select the optimal treatment dose, targeting the best balance between treatment benefit and adverse events.

421. 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. Lovshin at 263, Table 1 (“0.1-1.6 mg once weekly”). Patients desired fewer injections, as compared to the prior art liraglutide and exenatide treatments, requiring daily, and twice daily injections, respectively. *See* Vilsbøll at 4, Table 1. A POSA would have known from the prior art that semaglutide was an option that would be

³⁷ *See also* Lund at 610; WO '193 at 34:18; WO '328 at 1:16-17; Bhansali at 13; Novo Pipeline at 1-3.

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. Jimenez-Solem at 794 (“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.”); Knudsen 2004 at 4131 (“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.

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

423. As detailed above, Lovshin’s disclosure of a dosing range from 0.1 to 1.6 mg for semaglutide was ultimately the disclosure of, at most, 16 possible choices. However, even within the range of 16 possible doses, a POSA would

have envisioned no more than a handful as being the weekly semaglutide dose to use effectively in the long term, with those doses most likely being near the upper end of Lovshin's disclosed range, as described below. Further, as of the priority date, a POSA would have known that liraglutide (Victoza), has substantially the same amino acid backbone as semaglutide, was approved in January 2010, in doses of 0.6, 1.2, and 1.8 mg. *See* 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 2669. 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, 0.8 mg (with and without titration), and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657 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* NCT000851773 at 7.³⁸

³⁸ My citation to the dosing range disclosed by NCT00851773 is confirmatory of the dosing range disclosed by NCT00696657 because each bracketed the ultimate optimal treatment dose that would have been obvious to a POSA. My opinions related to the disclosed dose range within which the obvious dose

424. Further, from one or more of these disclosures (i.e., from WO '421, Lovshin, NCT00696657, and/or NCT00851773), a POSA would have expected that, by disclosing both a method of treating diabetes with semaglutide and a range of semaglutide doses to use in that method, the doses disclosed in the prior art would function for their stated purpose. The claimed 1.0 mg dose falls within the range of doses expected to work for treating type 2 diabetes. And, the '462 patent admits that identifying the claimed 1.0 mg dose of semaglutide in a method for treating type 2 diabetes would have been obvious:

[A]n “effective amount” of a GLP-1 agonist as used herein means an amount sufficient to cure, alleviate, or partially arrest the clinical manifestations of a given disease or state and its complications. An amount adequate to accomplish this is defined as “effective amount”. Effective amounts for each purpose will depend on the severity of the disease or injury as well as the weight and general state of the subject. *It will be understood that determining an appropriate dosage may be achieved using routine experimentation, by constructing a matrix of values and testing different points in the matrix, which is all within the ordinary skills of a trained physician or veterinary.*

'462 patent at 5:4-15 (emphasis added).

would have been found by a POSA would remain the same without citation to NCT00851773.

425. 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. Lovshin at 263, Table 1 (“0.1-1.6 mg once weekly”). And a POSA would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. Thus, at most, the disclosed range of doses would include no more than 16 options to try for administering to patients for treating type 2 diabetes, as described above. *See* Sections IX.A.1.a, IX.A.3.a.

426. 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.

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

427. 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 have substantially 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, e.g.*, Sections VII.D, VIII.G.6; Knudsen 2004, Fig. 3 (identifying residues “essential for binding” and “[u]nique for GLP-1,” all of which are found in semaglutide); Lund at 610, Table 2 (showing sequence homology for GLP-1 and several GLP-1 receptor agonists and the broad conservation of residues identified by Knudsen 2004). A POSA also would have known that liraglutide and semaglutide shared amino acids known from earlier work and available in the prior art, Knudsen 2004 at 4130, 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 Knudsen 2004 at 4130, Fig. 3; *Id.*, Fig. 2 (liraglutide sequence); '462 patent at 9:43-44 (admitting WO '537 at 48:4-22 (Example 4) disclosed semaglutide and therefore its sequence).

428. As further support, a POSA would have known that there were several other GLP-1-related compounds being studied in both human and preclinical trials, each of which was known to be effective to reduce blood

glucose, HbA_{1c} levels, and body weight, while avoiding the complication of hypoglycemia. *See* Lovshin at 263-66 (identifying, in addition to liraglutide, exenatide, AVE0010 (a modified exendin), albiglutide, taspoglutide, CJC-1134-PC, LY2189265, and LY2428757, several of which were once weekly formulations); *see also, e.g.*, 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 provide the same benefits, given that the several compounds all belonged to the same class of GLP-1 receptor agonists. Lovshin at 263-266; *see also* Knudsen 2004 at 4130, Figs. 1 and 2 (GLP-1 and liraglutide sequences); '462 patent at 9:43-44 (citing WO '537 at 48:4-22 (semaglutide sequence)); *see also* 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).

429. 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, 0.8 mg (with and without titration), and doses leading up to 1.6 mg (1.6 mg with titration), *see* NCT00696657 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* NCT000851773 at 7.³⁹ 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, and those trials were complete (see, e.g., Novo Pipeline at 1-3, Bhansali at 13) 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.,* Knudsen 2010b (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.,* Seino at 164 (dose-response

³⁹ My citation to the dosing range disclosed by NCT00851773 is confirmatory of the dosing range disclosed by NCT00696657 because each bracketed the ultimate optimal treatment dose that would have been obvious to a POSA. My opinions related to the disclosed dose range within which the obvious dose would have been found by a POSA would remain the same without citation to NCT00851773.

curve for HbA1c response versus liraglutide dose, showing greater treatment effect with the larger doses).

430. 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 treating type 2 diabetes with a 1.0 mg weekly dose of semaglutide.⁴⁰ *See also, e.g.,* Seino at 166 (“A clear dose

⁴⁰ I conclude that a POSA would have been motivated to use a once weekly 1.0 mg dose of semaglutide with a reasonable expectation of success that it would be effective to treat type 2 diabetes. I understand that the Court has determined that the preamble of claim 1, “[a] method for treating type 2 diabetes,” means that “the claimed administration is for the purpose of care and management of a patient with Type 2 diabetes” or “the claimed administration is intended to care for and manage a patient with Type 2 diabetes.” D.I. 148 at 2-3. I also understand that the Court construed that term so that it does not require any particular degree or minimum threshold of efficacy. My conclusion from the prior art therefore applies to the method for treating type 2 diabetes as the Court has interpreted that term (i.e., as not requiring any minimum degree of efficacy) and additionally goes beyond what the Court’s interpretation requires in terms of efficacy. That is, I believe the prior art would motivate a POSA to use a once-

response relationship for HbA1c reduction was shown in this study. All doses of liraglutide tested showed a degree of efficacy”). Thus, in my opinion, claim 1 of the ’462 patent would have been obvious to a POSA over WO ’537 in view of Lovshin.

b. Claim 3

431. Claim 2 of the ’462 patent depends from claim 1 and recites the additional limitation that “semaglutide is administered by parenteral administration.” Claim 3 of the ’462 patent depends from claim 2 and further recites the additional limitation that the parenteral administration occurs “by subcutaneous injection.”⁴¹

432. WO ’537 disclosed that “[p]arenteral administration [of semaglutide] may be performed by subcutaneous, intramuscular, intraperitoneal

weekly 1.0 mg semaglutide dose with a reasonable expectation that it would provide significantly more than a minimal level of efficacy in treating Type 2 diabetes.

⁴¹ Claim 3 actually recites, “[t]he method according to claim 2 [which depends from claim 1], wherein *the solution* is administered by subcutaneous injection.” ’462 patent at claim 3 (emphasis added). But neither claim 2 nor claim 1 recites “a solution.”

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

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

434. Regarding the subject matter of claim 3, WO ’537 disclosed that “[p]arenteral administration [of semaglutide] may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe,” and a POSA would have understood that the injection was of a solution. WO ’537 at 34:15-16; *see also id.* at 34:3-4 (preferably, controlled-release and sustained-release compositions are administered subcutaneously).

435. Thus, in addition to rendering obvious the subject matter of claim 1, in conjunction with Lovshin, and claim 2, WO ’537 further disclosed claim 3’s requirement that the parenteral administration occurs “by subcutaneous injection.” Therefore, in my opinion, claim 3 would have been obvious to a POSA over WO ’537 in view of Lovshin.

c. Claims 4, 5, and 7

436. It is my opinion that claims 1 and 3 of the '462 patent would have been obvious to a POSA over WO '537 in view of Lovshin, 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 and 3 of the '462 patent. However, I understand it is Dr. Dalby's opinion that the asserted art disclosed all formulation-related elements of claims 4, 5, and 7 of the '462 patent.

437. It is therefore my opinion that claims 4, 5, and 7 of the '462 patent would have been obvious to a POSA over WO '537 in view of Lovshin for the reasons addressed in Sections IX.B.3.a and b and by Dr. Dalby.

* * *

438. It is therefore my opinion that claims 1, 3, 4, 5, and 7 of the '462 patent would have been obvious to a POSA over WO '537 in view of Lovshin.

C. All Claims of the '462 Patent Are Invalid for Lack of Written Description if They Would not have been Obvious

439. I understand that the test for written description is whether the disclosure of the application relied upon reasonably conveys to those skilled in the art that the inventor had possession of the claimed subject matter as of the filing date. I further understand that the written description must clearly allow

persons of ordinary skill in the art to recognize that the inventor invented what is claimed, and that it is the specification itself that must demonstrate possession.

440. I understand that the disclosure of a broad range of values does not by itself provide written description support for a particular value within that range. I understand instead that where a specification discloses a broad range of values and a value within that range is claimed, the disclosure must allow one skilled in the art to immediately discern the limitation at issue in the claims. I understand that it is not enough that a patent's specification merely makes obvious the claimed invention. In other words, I understand it is said that one cannot disclose a forest in the original application, and then later pick a tree out of the forest and say, "Here is my invention."

441. Finally, I understand that the written description requirement is not met simply because the claim language appears in the same way in the specification. I understand that this is so because the written description requirement provides an incentive for "actual invention," and a mere wish or plan for obtaining the claimed invention does not reflect actual invention and is therefore not adequate written description.

442. Here, the '462 patent's specification discloses a broad range of dose values but does not show that the inventors had actual possession of the specifically claimed 1.0 mg dose. *See* '462 Patent at 3:41-55, 15:16-18, 17:20-34;

see also '462 file history (EP12174535 priority document) at -4254 (3:5-15), -4269 (18:26-27), -4272 (21:16-25) (same). No working example is provided in the specification relating to the 1.0 mg dose. The specification instead focuses heavily on the 0.7 mg dose, which is what the initially filed claims were directed to. *Id.* at 1:41-43, 1:51-54, 1:64-66, 4:7-43, 16:58-64, 20:17-27, 20:31-44; *see also* '462 file history (EP12174535 priority document) at -4252, -4254-55, -4271, -4276-77 (same).

443. Though the specification describes a clinical study testing semaglutide doses ranging from 0.1 mg through 1.6 mg, that study does not specifically describe the 1.0 mg dose, and describes only individual step doses. *See* '462 patent at 20:61–23:26, Table 1 (disclosing tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg)); *see also* '462 file history (EP12174535 priority document) at -4277-78; *see also* '462 patent at Fig. 1 (disclosing change in HbA_{1c} for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg)); Fig. 2 (disclosing change in HbA_{1c} over time for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg)); Fig. 3A (disclosing percent of

subjects with $\text{HbA}_{1c} \leq 6.5\%$ for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg), designated arms B-G, respectively); Fig. 3B (disclosing percent of subjects with $\text{HbA}_{1c} \leq 7\%$ for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg), designated arms B-G, respectively); Fig. 4 (disclosing change in body weight over time for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg)); Fig. 5 (disclosing change in body weight for tested doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration (steps of 0.4 mg and 0.8 mg), and 1.6 mg with titration (steps of 0.4 mg from 0.4 to 0.8 to 1.2 to 1.6 mg)); *see also* '462 file history at -4290 (EP12174535 priority document disclosing only Fig. 1 with doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration).

444. In fact, the only references to a 1.0 mg dose in the specification are passing references made in the context of “catch all” phrases reciting doses used in “embodiments” of the invention not connected to a specific treatment. For instance, the specification recites, “[i]n one embodiment the GLP-1 agonist is administered in an amount per week of at least 0.8 mg, at least 0.9 mg, or at least

1.0 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg. In one embodiment the GLP-1 agonist is administered in an amount per week of at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg.” ’462 patent at 3:41-47; *see also* ’462 file history at -4254 (EP12174535 priority document at 3:5-9). But this passage does not identify the “GLP-1 agonist” as semaglutide, does not identify the administration as once weekly, and does not identify the purpose or intent of the administration as treating diabetes. Each of these elements is required by claim 1 of the ’462 patent.

445. In another passage, the ’462 patent recites that “[i]n one embodiment the GLP-1 agonist is administered in an amount per week *equivalent to* at least 0.8 mg, at least 0.9 mg, or at least 1.0 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.1 mg, at least 1.2 mg, or at least 1.3 mg semaglutide. In one embodiment the GLP-1 agonist is administered in an amount per week equivalent to at least 1.4 mg, at least 1.5 mg, or at least 1.6 mg semaglutide.” ’462 patent at 3:48-55 (emphasis added); *see also* ’462 file history at -4254 (EP12174535 priority document at 3:10-15). But here, the passage does not identify what it means to be “equivalent to” a 1.0 mg dose of semaglutide, does not identify the administration as once weekly, and does not identify the purpose

or intent of the administration as treating diabetes. Each of these elements is required by claim 1 of the '462 patent.

446. In another set of passages, the inventor of the '462 patent provided a series of statements reciting numerous possible combinations of treatment parameters, not identifying any of them, in whole, as a treatment method using 1.0 mg semaglutide once weekly to treat Type 2 diabetes. *See* '462 patent at 16:54-20:54 (identifying 40 different aspects of “embodiments of the invention”); *see also* '462 file history at -4271-77 (EP12174535 priority document) (same); *see also* '462 patent at 17:20-28 (reciting “method[s] according to any one of the preceding embodiments, wherein said GLP-1 agonist is administered in an amount of at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, per week,” or “wherein said GLP-1 agonist is administered in an amount equivalent to at least 0.8 mg, at least 1.0 mg, or at least 1.2 mg, such as at least 1.4 mg or at least 1.6 mg, semaglutide per week”); *see also* '462 file history at -4272 (EP12174535 priority document) (same). These ten possible dose amounts are preceded by “embodiments” identifying treatment of at least seven different conditions, GLP-1 agonists having one of at least ten different half-lives, and administering the GLP-1 agonist on one of at least five different treatment schedules. '462 patent at 16:58-

17:19;⁴² *see also* '462 file history at -4271-72 (EP12174535 priority document) (same). The dose amounts are then followed by “embodiments” identifying, for example, at least four possible GLP-1 agonists, simultaneous or sequential administration with another therapeutic agent, and use of any one of hundreds of millions of possible GLP-1 peptides. *See* '462 patent at 17:50-18:32; *see also* '462 file history at -4272-74 (EP12174535 priority document) (same).

447. In short, by describing so many isolated portions of “embodiments,” a POSA would not have understood the inventor to have described any particular embodiment encompassing selected isolated portions in a way that aligns with the claimed method.

448. Further, I understand that when a patent repeatedly describes a certain set of features as “the invention,” a POSA is entitled to understand that the claimed invention is directed to those features.

449. Here, when the inventor of the '462 patent did focus on describing “the invention” of the patent, even in a way that was related to semaglutide, the inventor never recited a combination of treatment elements that aligned with the claims’ requirements that the allegedly inventive method be used to treat Type

⁴² Just this brief list provides 3,500 possible combinations of claim elements from which the 1.0 mg once weekly dose of semaglutide must be selected.

2 diabetes with 1.0 mg semaglutide once weekly. *See, e.g., '462 patent at 2:63-3:2* (“*In one embodiment the invention relates to a method for reduction of HbA1c or for prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes, said method comprising administration of a GLP-1 agonist to a subject in need thereof in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.*” (emphasis added)); *see also '462 file history at -4253 (EP12174535 priority document) (same); see also, e.g., '462 patent at 4:8-14* (“*In one embodiment the invention relates to a GLP-1 agonist for use in the reduction of HbA1c or for use in the prevention or treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes comprising administering a GLP-1 agonist in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week.*”); *see also '462 file history at -4254 (EP12174535 priority document) (same).* In each case, “the invention” did not recite once weekly dosing, and did not recite the use of 1.0 mg of semaglutide. Indeed, each recited “embodiment [of] the invention” only requires the use of an unidentified “GLP-1 agonist” in an amount “equivalent to” 0.7 mg of semaglutide, and does not require the actual use of either semaglutide or a 1.0 mg dose.

450. Thus, in my opinion, nowhere does the '462 patent include a written description sufficient to show that the named inventor was in possession of the complete invention claimed in the '462 patent, which requires at least administering 1.0 mg semaglutide once weekly for the purpose of care and management of a patient with Type 2 diabetes or with the intent to care for and manage a patient with Type 2 diabetes.

451. Therefore, claims 1, 3, 4, 5, and 7 of the '462 patent are invalid for lack of written description for at least the 1.0 mg limitation, in addition to the other claim elements recited above. Further, because the disclosure of the EP12174535 priority document shares with the '462 patent the same descriptive deficiencies, the EP12174535 priority document cannot provide written description support for the asserted claims.

X. RESERVATION OF RIGHTS

452. I reserve the right to supplement and/or expand on the opinions I have set forth in this report based on the information I have reviewed and/or based on any additional information produced in this litigation, any relevant claim construction, in response to any expert reports submitted on behalf of Plaintiffs, or any other circumstances that may impact my opinions.

453. Moreover, during this litigation I may rely upon documents and/or other materials produced in the litigation, 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: March 19, 2024

By:

John Bantle, MD
Dr. John Bantle

EXHIBIT A

Curriculum Vitae

JOHN PETER BANTLE, M.D.

October 2023

Office Address: MMC 101
University of Minnesota
Minneapolis, MN 55455

Universities Attended:

1965 - 1968 University of Minnesota, Minneapolis, Minnesota
1968 - 1972 University of Minnesota Medical School, Minneapolis, Minnesota

Degrees:

1970 Bachelor of Science
1972 Doctor of Medicine

Professional Training:

Internship

Rotating Internship with medicine emphasis
Cleveland Metropolitan General Hospital
Cleveland, Ohio
July 1972 - June 1973

Residency

Internal Medicine
Mayo Clinic
Rochester, Minnesota
July 1973 - September 1975

Internal Medicine (Registrar)
Dunedin Public Hospital
Dunedin, New Zealand
November 1975 - February 1976

Fellowship

Endocrinology and Metabolism
University of Minnesota
Minneapolis, Minnesota
July 1976 - June 1978

State License: Minnesota (No. 21141)

Board Certification:

1975 American Board of Internal Medicine (certification number 50035)
1979 Endocrinology and Metabolism (certification number 50035)

Professional Experience:

Instructor, Department of Medicine
University of Minnesota Medical School
July 1978 - June 1979

Assistant Professor, Department of Medicine
University of Minnesota Medical School
July 1979 - June 1987

Associate Professor, Department of Medicine
University of Minnesota Medical School
July 1987 - June 1996

Professor, Department of Medicine
University of Minnesota Medical School
July 1996 - December 2016

Professor Emeritus
University of Minnesota Medical School
January 2017 - present

Associate Director, General Clinical Research Center
University of Minnesota Medical School
July 1983 - November 2009

Medical Staff Clinical Service Chief for Internal Medicine
Fairview-University Medical Center
January 2001 - May 2007

Interim Director, Division of Endocrinology and Diabetes
Department of Medicine
University of Minnesota Medical School
October 2008 - April 2010

Director, Division of Endocrinology and Diabetes
Department of Medicine
University of Minnesota Medical School
May 2010 – March 2015

Leader, Clinical Research Implementation Services (CRIS)
Clinical and Translational Science Institute (CTSI)
University of Minnesota
August 2011 - 2013

Membership in Organizations:

American Diabetes Association
The Endocrine Society

Honors and Awards:

Alpha Omega Alpha, University of Minnesota Medical School, 1972
Nominated for Minnesota Medical Foundation Distinguished Clinical Teacher Award in 1992 and 1993
Recipient of Department of Medicine 2002 Clinical Excellence Award
Recipient of Department of Medicine 2004 Clinical Excellence Award
Recipient of Department of Medicine 2011 Clinical Excellence Award
Named in the Minneapolis/St. Paul Magazine surveys of Twin Cities doctors and nurses as a leading doctor in his specialty; i.e., one they would pick for their own care, in 1992, 1994, 1996, 1999, 2000, 2001, 2002, 2004, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and 2017.
Selected by peers to be included in Best Doctors in America 1996, 1997, 1998, 1999, 2000, 2001, 2002, 2003, 2004, 2005, 2006, 2007, 2008, 2009, 2010, 2011, 2012, 2013, 2014, 2015, 2016 and 2017.

Service at the National Level

Member of the American Diabetes Association Committee which developed 1994 diabetes nutrition recommendations
Member of the American Diabetes Association Committee which developed the 1998 standards of care for people with diabetes
Co-Chair of the American Diabetes Association Committee which developed 2002 diabetes nutrition recommendations

Co-Chair of the American Diabetes Association Committee which developed 2006 diabetes nutrition recommendations

Service to the University

Elected member University of Minnesota Physicians Board of Directors (2006 - 2009)

Elected member University of Minnesota Senate (1999 - 2002, 2007 - 2010)

Service to the Department of Medicine

Medical Staff Clinical Service Chief (2001 - 2007)

Elected member Department of Medicine Board of Governors (two terms, 1999 - 2005)

Member Promotion and Tenure Committee (1997 - 2003)

Medical Director, Diabetes Education and Self-Management Program (1995 - 2000)

Selected Regional, National and International Lectures and Symposia:

Postprandial Responses to Meals Containing Sugars and Starches. NIH Seminar of Nutrition Coordinating Committee, Bethesda, MD, September 8, 1983.

Metabolic Effects of Dietary Fructose. American Medical Association Resource Conference on Fructose, Chicago, IL, October 1-2, 1984.

Effects of Dietary Sucrose and Fructose. NIH Diabetes Update, Bethesda, MD, March 30, 1985.

The Glycemic Effects of Dietary Carbohydrates. NIH Consensus Development Conference on Diet and Exercise in NIDDM, Bethesda, MD, December 8-10, 1986.

Dietary Fructose and Sucrose in People with Diabetes. UCSF and Northern California American Diabetes Association Affiliate Symposium on Sweeteners in Diabetes, San Francisco, CA, March 20, 1987.

Dietary Carbohydrates and their Effect on Plasma Glucose. American Diabetes Association Symposium on Nutrition and Metabolism, San Francisco, CA, October 6-8, 1988.

Current Controversy: Carbohydrate and Fat. American Diabetes Association Council on Nutritional Sciences and Metabolism, Las Vegas, NV, June 12, 1993.

Diabetes Control and Complications Update. American Dietetic Association National Meeting, Anaheim, CA, October 28, 1993.

Nutritional Issues in the Management of NIDDM. American Diabetes Association Annual Advanced Postgraduate Course, Boston, MA, January 28-30, 1994.

Controversies in the Nutritional Management of Diabetes. University of Iowa, Iowa City, IA, April 27, 1995.

Current Trends in Obesity Management for Diabetes. American Diabetes Association Utah Affiliate, Salt Lake City, UT, May 12, 1997.

Health Implications of Obesity: A Focus on Diabetes. American Diabetes Association Annual Meeting, Boston, MA, June 21, 1997.

Current Nutrition Recommendations of the American Diabetes Association. American College of Nutrition Annual Meeting, New York, NY, September 27, 1997.

Obesity and Type 2 Diabetes. Video Conference sponsored by the University of Minnesota and the American Diabetes Association, New York, NY, February 25, 1998.

Intensive Treatment of Type 1 Diabetes Mellitus. St. Louis University, St. Louis, MO, October 5, 2001.

Evidence Based Nutrition Recommendations for Diabetes: 2001. American Dietetic Association National Meeting, St. Louis, MO, October 21, 2001.

Glycemic Index: Scientific Merit and Clinical Utility. American Diabetes Association Annual Meeting, San Francisco, CA, June 15, 2002.

A Combination of Food Based Strategies and Pharmacotherapy for Weight Reduction in Type 2 Diabetes. European Congress on Obesity, Helsinki, Finland, May 30, 2003.

Prevention and Treatment of Diabetes Mellitus. St. Louis University, St. Louis, MO, November 7, 2003.

Weight Loss as Primary Therapy for Type 2 Diabetes Mellitus. National (Mexican) Congress on Diabetes, Acapulco, Mexico, March 10, 2005.

Is Fructose the Optimal Low Glycemic Index Sweetener? Nestle Symposium on Nutritional Management of Diabetes Mellitus and Dysmetabolic Syndrome, Hangzhou, China, October 30 – November 2, 2005 (meeting Co-Chairman).

Do Fructose and Sugar Alcohols make a Difference in Diabetes and Weight Control? American Diabetes Association Annual Advanced Postgraduate Course, San Francisco, CA, February 11, 2006.

Nutrition Guidelines for Diabetes – A Focus on Carbohydrates. Satellite Symposium, International Diabetes Federation World Congress, Cape Town, South Africa, December 6, 2006.

Keynote: Management of Type 2 Diabetes. University of Nebraska conference Management of Diabetes and Complications, Omaha, NE, March 30, 2007.

Factors to Consider when Conducting Research on Fructose and Metabolic Syndrome and Diabetes. ILSI North America and United States Department of Agriculture Symposium on The State of the Science on Dietary Sweeteners Containing Fructose, Beltsville, MD, March 19-19, 2008.

Non-Pharmacologic Therapy of Type 2 Diabetes. Meet-the-Professor Session. Endocrine Society Annual Meeting, San Francisco, CA, June 16, 2008.

The Diabetes Epidemic. CME Institute, Maui, HI, March 1, 2010.

Bariatric Surgery and Type 2 Diabetes: For Whom, How and At What Point in the Natural History? American Diabetes Association 58th Annual Advanced Postgraduate Course, New York, NY, February 27, 2011.

Clinical Research Strategies for Fructose Metabolism, NIH, Bethesda, MD, November 13-14, 2012 (Session I Chair).

Metabolic Surgery: Advantages and Disadvantages. American Diabetes Association 60th Annual Advanced Postgraduate Course, New York, NY, February 24, 2013.

Bariatric Surgery as Treatment for Type 2 Diabetes Mellitus: An Endocrinologist's Perspective. Fifth Asian Diabetes Surgery Summit, Taipei, Taiwan, October 25, 2014.

Post-Bariatric Surgery Hypoglycemia. Meet-the-Professor Session. Endocrine Society Annual Meeting, Boston, MA, April 2, 2016.

Post-Bariatric Surgery Hyperinsulinemic Hypoglycemia. University of Indiana, Indianapolis, IN, February 8, 2017.

Medical Approach to Obesity Management. Seventh Emirates Diabetes and Endocrine Congress. Dubai, United Arab Emirates, February 17, 2017.

Areas of Research Interest:

1. Intensive treatment of diabetes mellitus
2. Dietary treatment of diabetes mellitus
3. Metabolic effects of dietary carbohydrates
4. Treatment of obesity

Chronology of Grants and Research Support as Principal Investigator or Co-Principal Investigator:

Archer, Daniels, Midland Foundation (1981-1983) \$12,000
 "Plasma Glucose Response to Various Forms of Dietary Carbohydrate"

Sandoz, Inc. (1983-1984) \$7,000
 "Potassium Clearance in Renal Transplant Recipients Receiving Cyclosporine"

American Diabetes Association, Inc. (1983-1985) \$49,568
 "Comparison of Fructose, Sucrose and Starch in the Diabetic Diet"

The Estee Corporation (1983-1985) \$14,000
 "Comparison of Fructose, Sucrose and Starch in the Diabetic Diet"

Sandoz, Inc. (1984-1986) \$17,920
 "Effects of Cyclosporine on the Renin-Angiotensin-Aldosterone System"

American Diabetes Association, Minnesota Affiliate (1985-1986) \$5,000
 "Comparison of the Diabetic Exchange Lists and the Glycemic Index of Foods"

Public Health Service, NIH NIDDK (1985-1996) \$2,732,116
 "Diabetes Control and Complications Trial (DCCT)"

Sandoz, Inc. (1987-1988) \$15,000
 "Trial of Alpha Adrenergic Blockade to Prevent Cyclosporine Nephrotoxicity"

The International Fructose Association (1987-1991) \$100,000
 "Metabolic Effects of Chronic Dietary Fructose and Sucrose Consumption"

Eli Lilly and Company (1989) \$4,700
 "Effects of Rotating Insulin Injection Sites in Type I Diabetic Subjects"

Roerig Division, Pfizer Incorporated (1990-1992) \$100,385
 "Effects of Two Different Dietary Regimens on Glucose and Lipid Metabolism in Glipizide Treated Patients with NIDDM"

Integ, Inc. (1996-1997) \$35,933
 "The Use of Dermal Interstitial Fluid for Glucose Monitoring"

American Diabetes Association (1997-1998) \$72,406
 "Pharmacologic Induction of Weight Loss to Treat Type 2 Diabetes Mellitus"

Smith Kline Beecham Pharmaceuticals (1998) \$10,000
 "Plasma Serotonin in Fenfluramine and Phentermine Treated Patients"

Medtronic, Inc. (1999-2000) \$29,834
 "ECG Analysis for Blood Glucose Monitoring"

Abbott Laboratories and Slim Fast Foods Company (2000-2003) \$333,297
 "Combination Weight Loss Therapy for Type 2 Diabetes Mellitus"

Public Health Service, NIH NHLBI (2001-2010) \$1,115,950
 "Bypass Angioplasty Revascularization 2 Diabetes (BARI 2D)"

Public Health Service, NIH NIDDK (2002-2022) \$1,393,783 for most recent 5 years
 "Action for Health in Diabetes Extension Study (Look AHEAD)"
 Role: Co-Principal Investigator,

Public Health Service, NIH NIDDK (7/1/2017-6/30/2022) \$157,894 for current year
 "Epidemiology of Diabetes Intervention and Complications (EDIC)"
 Role: Principal Investigator, 6% effort

Publications in Peer Reviewed Journals

1. Bantle JP, Dillmann WH, Oppenheimer JH, Bingham C, Runger GC. Common clinical indices of thyroid hormone action: relationships to serum free T₃ concentration and estimated nuclear occupancy. *J Clin Endocrinol Metab* 1980;50:286-293.
2. Bantle JP, Oppenheimer JH, Schwartz HL, Hunninghake DB, Probstfield JL, Hanson RF. TSH response to TRH in euthyroid, hypercholesterolemic patients treated with graded doses of dextrothyroxine. *Metabolism* 1981;30:63-66.
3. Schuster LD, Bantle JP, Oppenheimer JH, Seljeskog EL. Acromegaly: reassessment of the long-term therapeutic effectiveness of transphenoidal pituitary surgery. *Ann Intern Med*. 1981;95:172-174.
4. Bantle JP, Seelig S, Mariash CN, Ulstrom RA, Oppenheimer JH. Resistance to thyroid hormones: a disorder frequently confused with Graves' disease. *Arch Intern Med* 1982; 142:1867-1871. Summarized in 1984 Year Book of Medicine.
5. Mitchell JE, Bantle JP. Metabolic and endocrine investigations in women of normal weight with the bulimia syndrome. *Biol Psychiatry* 1983;18:355-365.
6. Bantle JP, Beyer S, Oppenheimer JH. Recurrent episodes of spontaneously resolving hyperthyroidism due to thyroiditis. *Minn Med* 1983;66:295-297.
7. Bantle JP, Laine DC, Castle GW, Thomas JW, Hoogwerf BJ, Goetz FC. Postprandial glucose and insulin responses to meals containing sugars or starches in normal and diabetic subjects. *N Engl J Med* 1983;309:7-12. Summarized in 1984 Year Book of Medicine.
8. Hoogwerf BJ, Barbosa JJ, Bantle JP, Laine DC, Goetz FC. Urinary C-peptide as a measure of beta cell function following a mixed meal in healthy subjects: comparison of four hour urine C-peptide with serum insulin and plasma C-peptide. *Diabetes Care* 1983; 6:488-492.
9. Bantle JP, Laine DC, Hoogwerf BJ, Goetz FC. The potential usefulness of postprandial urine C-peptide measurement in classifying diabetic patients. *Diabetes Care* 1984;7:202-203 (letter).
10. Hoogwerf BJ, Bantle JP, Kuba K, Frantz ID, Hunninghake DB. Treatment of type III hyperlipoproteinemia with four different treatment regimens. *Atherosclerosis* 1984;51: 251-259.
11. Mascioli SR, Bantle JP, Freier EF, Hoogwerf BJ. Artifactual elevation of serum creatinine due to fasting. *Arch Intern Med* 1984;144:1575-1576. Summarized in 1985 Year Book of Medicine.
12. Bantle JP, Hunninghake DB, Frantz ID, Kuba K, Mariash CN, Oppenheimer JH. Comparison of the effectiveness of thyrotropin-suppressive doses of D- and L-thyroxine in the treatment of hypercholesterolemia. *Am J Med* 1984;77:475-481.
13. Bantle JP, Nath KA, Sutherland DER, Najarian JS, Ferris TF. Effects of cyclosporine on the renin-angiotensin-aldosterone system and potassium clearance in renal transplant recipients. *Arch Intern Med* 1985;145:505-508. Summarized in 1986 Year Book of Medicine.
14. Beyer HS, Bantle JP, Mariash CN, Steffes MW, Seljeskog EL, Oppenheimer JH. Use of the dexamethasone-adrenocorticotropin test to assess the requirement for continued glucocorticoid replacement therapy after pituitary surgery. *J Clin Endocrinol Metab* 1985;60:1012-1018.
15. Bantle JP, Lee CKK, Levitt SH. Thyroxine administration during radiation therapy to the neck does not prevent subsequent thyroid dysfunction. *Int J Radiat Oncol Biol Phys*. 1985;11:1999-2002.
16. Hoogwerf BJ, Bantle JP, Gaenslen HE, Greenberg BZ, Senske BJ, Francis R, Goetz FC. Infusion of synthetic human C-peptide does not affect plasma glucose, serum insulin, or plasma glucagon in healthy subjects. *Metabolism* 1986;35:122-125.

17. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT): design and methodologic considerations for the feasibility phase. *Diabetes* 1986;35:530-545.
18. Bantle JP, Laine DC, Thomas JW. Metabolic effects of dietary fructose and sucrose in type I and type II diabetic subjects. *JAMA* 1986;256:3241-3246.
19. The DCCT Research Group. The Diabetes Control and Complications Trial (DCCT): results of the feasibility study (phase II). *Diabetes Care* 1987;10:1-19.
20. Fish LH, Schwartz HL, Cavanaugh J, Steffes MW, Bantle JP, Oppenheimer JH. Replacement dose, metabolism, and bioavailability of levothyroxine in the treatment of hypothyroidism: Role of T3 in pituitary feedback in man. *N Engl J Med* 1987;316:764-770.
21. Laine DC, Thomas JW, Levitt MD, Bantle JP. Comparison of the predictive capabilities of the diabetic Exchange Lists and the Glycemic Index of Foods. *Diabetes Care* 1987; 10:387-394.
22. Bantle JP, Boudreau RJ, Ferris TF. Suppression of plasma renin activity by cyclosporine. *Am J Med* 1987;83:59-64.
23. Bantle JP, Laine DC. Day-to-day variation in glycemic control in type I and type II diabetes mellitus. *Diabetes Res* 1988;8:147-149.
24. Bantle JP, Paller MS, Boudreau RJ, Olivari MT, Ferris TF. Long-term effects of cyclosporine on renal function in organ transplant recipients. *J Lab Clin Med* 1990;115:233-240.
25. Bantle JP, Weber MS, Rao SMS, Chattopadhyay MK, Robertson RP. Rotation of the anatomic regions used for insulin injections and day-to-day variability of plasma glucose in type I diabetic subjects. *JAMA* 1990;263:1802-1806. Summarized in 1991 Year Book of Medicine.
26. The DCCT Research Group. Diabetes Control and Complications Trial (DCCT): Update. *Diabetes Care* 1990;13:427-433.
27. Swanson JE, Laine DC, Thomas W, Bantle JP. Metabolic effects of dietary fructose in healthy subjects. *Am J Clin Nutr* 1992;55:851-856.
28. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary fructose in diabetic subjects. *Diabetes Care* 1992;15:1468-1476.
29. The DCCT Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977-986. Summarized in 1994 Year Book of Medicine.
30. Bantle JP, Swanson JE, Thomas W, Laine DC. Metabolic effects of dietary sucrose in type II diabetic subjects. *Diabetes Care* 1993;16:1301-1305.
31. Bantle JP, Neal L, Frankamp LM. Effects of the anatomical region used for insulin injections on glycemia in type I diabetic subjects. *Diabetes Care* 1993;16:1592-1597.
32. Garg A, Bantle JP, Henry RR, Coulston AM, Griver K, Raatz SK, Brinkley L, Chen YD, Grundy SM, Huet BA, Reaven GM. Long-term effects of varying carbohydrate content of diet in patients with non-insulin-dependent diabetes mellitus. *JAMA* 1994;271:1421-1428.
33. Campbell JA, Schmidt BA, Bantle JP. Sucralfate and the absorption of L-thyroxine. *Ann Intern Med* 1994;121:152 (letter).
34. The DCCT Research Group. Implementation of conventional and intensive treatment in the Diabetes Control and Complications Trial. *Diabetes Care* 1995;18:361-375.
35. The DCCT Research Group. The effect of intensive diabetes treatment on the progression of diabetic retinopathy in insulin-dependent diabetes mellitus: the Diabetes Control and Complications Trial. *Arch Ophthalmol* 1995;113:36-51.
36. The DCCT Research Group. The effect of intensive diabetes therapy on the development and progression of neuropathy in the Diabetes Control and Complications Trial. *Ann Intern Med* 1995;122:561-568.
37. The DCCT Research Group. The effect of intensive therapy on the development and progression of diabetic nephropathy in the Diabetes Control and Complications Trial. *Kidney Int* 1995;47:1703-1720.

38. Bhatia S, Ramsay NKC, Bantle JP, Martens A, Robison LL. Thyroid abnormalities after therapy for Hodgkins Disease in childhood. *The Oncologist* 1996;1:62-67.
39. Bantle JP, Thomas W. Glucose monitoring using dermal interstitial fluid. *J Lab Clin Med* 1997;130:436-441.
40. Redmon B, Raatz SR, Bantle JP. Valvular heart disease associated with fenfluramine-phentermine. *N Engl J Med* 1997; 337:1773-1774 (letter).
41. Georgopoulos A, Bantle JP, Swaim WR, Parker SJ. Differences in the metabolism of postprandial lipoproteins during a high monounsaturated fat versus a high carbohydrate diet in patients with IDDM. *Arterioscler Thromb Vasc Biol* 1998;18:773-782.
42. The EDIC Research Group. Epidemiology of Diabetes Intervention and complications (EDIC): Design and implementation of a long-term follow-up of the Diabetes Control and Complications Trial cohort. *Diabetes Care* 1999;22:99-111.
43. Redmon JB, Raatz SK, Kwong C, Swanson J, Thomas JW, Bantle JP. Pharmacologic induction of weight loss to treat type 2 diabetes mellitus. *Diabetes Care* 1999;22:896-903.
44. The EDIC Research Group. The effect of intensive diabetes treatment on carotid artery wall thickness in the Epidemiology of Diabetes Interventions and Complications (EDIC). *Diabetes* 1999;48:383-390.
45. The DCCT/EDIC Research Group. Retinopathy and nephropathy in patients with type 1 diabetes four years after a trial of intensive therapy. *N Engl J Med* 2000;342:381-389.
46. Rothman RB, Redmon JB, Raatz SK, Kwong CA, Swanson JE, Bantle JP. Chronic treatment with phentermine combined with fenfluramine lowers plasma serotonin. *Am J Cardiol* 2000;85:913-915.
47. The DCCT Research Group. Effects of pregnancy on microvascular complications in the Diabetes Control and Complications Trial. *Diabetes Care* 2000;23:1084-1091.
48. Bantle JP, Raatz SK, Georgopoulos A, Thomas W. Effects of dietary fructose on plasma lipids in healthy subjects. *Am J Clin Nutr* 2000;72:1128-1134.
49. Georgopoulos A, Bantle JP, Noutsou M, Hoover HA. A high carbohydrate versus a high monounsaturated fatty acid diet lowers the atherogenic potential of big VLDL particles in patients with type 1 diabetes. *J Nutr* 2000;130:2503-2507.
50. The DCCT/EDIC Research Group. Intensive diabetes therapy and carotid intima-media thickness in type 1 diabetes mellitus. *N Engl J Med* 2003;348:2294-2303.
51. The DCCT/EDIC Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy. *JAMA* 2003; 290:2159-2167.
52. Redmon JB, Raatz SA, Reck KP, Swanson JE, Kwong CA, Fan Q, Thomas W, Bantle JP. A combination of weight loss therapies for subjects with type 2 diabetes mellitus. *Diabetes Care* 2003;26:2505-2511.
53. Look AHEAD Research Group. Look AHEAD (Action for Health in Diabetes): design and methods for a clinical trial of weight loss for the prevention of cardiovascular disease in type 2 diabetes. *Control Clin Trials* 2003;24:610-628.
54. Mucha GT, Merkel S, Thomas W, Bantle JP. Fasting and insulin glargine in persons with type 1 diabetes mellitus. *Diabetes Care* 2004;27:1209-1210.
55. Redmon JB, Reck KP, Raatz SK, Swanson JE, Kwong CA, Hong J, Thomas W, Bantle JP. Two year outcome of a combination of weight loss therapies for type 2 diabetes. *Diabetes Care* 2005;28:1311-1315.
56. Raatz, SK, Torkelson CJ, Redmon JB, Reck KP, Kwong CA, Swanson JE, Chengcheng L, Thomas W, Bantle JP. Reduced glycemic index and glycemic load diets do not increase the effects of energy restriction on weight loss and insulin sensitivity in obese men and women. *J Nutr* 2005;135:2387-2391.
57. Shah M, Adams-Huet B, Bantle JP, Henry RR, Griver KA, Raatz SK, Brinkley LJ, Reaven GM, Garg A. Effect of a high-carbohydrate versus a high-cis-monounsaturated fat diet on blood pressure in patients with type 2 diabetes. *Diabetes Care* 2005;28:2607-2612.

58. The DCCT/EDIC Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. *N Engl J Med* 2005;353:2643-2653.
59. Brooks MM, Frye RL, Genuth S, Detre KM, Nesto R, Sobel BE, Kelsey SF, Orchard TJ for the BARI 2D Trial Investigators. Hypotheses, design and methods for the bypass angioplasty revascularization investigation 2 diabetes (BARI 2D) trial. *Am J Cardiol* 2006;97[suppl]:9G-19G.
60. Look AHEAD Research Group. The Look AHEAD study: a description of the lifestyle intervention and the evidence supporting it. *Obesity* 2006;14:737-752.
61. Bantle JP, Ikramuddin S, Kellogg TA, Buchwald H. Hyperinsulinemic hypoglycemia developing late after gastric bypass. *Obesity Surgery* 2007;17:592-594.
62. Look AHEAD Research Group. Reduction in weight and cardiovascular disease risk factors in individuals with type 2 diabetes. *Diabetes Care* 2007;30:1374-1383.
63. Bantle AE, Thomas W, Bantle JP. Metabolic effects of alcohol in the form of wine in persons with type 2 diabetes mellitus. *Metabolism* 2008;57:241-245.
64. Bertoni AG, Clark JM, Feeney P, Yanovski SZ, Bantle J, Montgomery B, Safford MM, Herman WH, Haffner S and the Look AHEAD Research Group. Suboptimal control of glycemia, blood pressure, and LDL cholesterol in overweight adults with diabetes: the Look AHEAD Study. *J Diabetes Complications* 2008;22:1-9.
65. BARI 2D Study Group. Baseline characteristics of patients with diabetes and coronary artery disease enrolled in the Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial. *Am Heart J* 2008;156:528-536.
66. Kellogg TA, Bantle JP, Leslie DB, Redmon JB, Slusarek B, Swan T, Buchwald H, Ikramuddin S. Postgastric bypass hyperinsulinemic hypoglycemia syndrome: characterization and response to a modified diet. *Surg Obes Relat Dis* 2008;4:492-499.
67. BARI 2D Study Group. A randomized trial of therapies for type 2 diabetes and coronary artery disease. *N Engl J Med* 2009;360:2503-2515.
68. The DCCT/EDIC Research Group. Modern-day clinical course of type 1 diabetes mellitus after 30 years' duration. *Arch Intern Med* 2009;169:1307-1316.
69. Look AHEAD Research Group. Long-term effects of a lifestyle intervention on weight and cardiovascular risk factors in individuals with type 2 diabetes. *Arch Intern Med* 2010;170:1566-1575.
70. The DCCT/EDIC Research Group. Intensive diabetes therapy and glomerular filtration rate in type 1 diabetes. *N Engl J Med* 2011;365:2366-2376.
71. Abdelmalek MF, Lazo M, Horska A, Bonekamp S, Lipkin EW, Balasubramanyam A, Bantle JP, Johnson RJ, Diehl AM, Clark JM and the Fatty Liver Subgroup of the Look AHEAD Research Group. Higher dietary fructose is associated with impaired hepatic ATP homeostasis in obese individuals with type 2 diabetes. *Hepatology* 2012;56:952-960.
72. Gregg EW, Chen H, Wagenknecht LE, Clark JM, Delahanty LM, Bantle J, Pownall HJ, Johnson KC, Safford M, Kitabchi AE, Pi-Sunyer FX, Wing RR, Bertoni AG and the Look AHEAD Research Group. Association of an intensive lifestyle intervention with remission of type 2 diabetes. *JAMA* 2012;308:2489-2496.
73. Ikramuddin S, Korner J, Lee WJ, Connett JE, Inabnet WB, Billington CJ, Thomas AJ, Leslie DB, Chong K, Jeffery RW, Ahmed L, Vella A, Chuang LM, Bessler M, Sarr MG, Swain JM, Laqua P, Jensen MD, Bantle JP. Roux-en-Y gastric bypass vs intensive medical management for control of type 2 diabetes, hypertension and hyperlipidemia: The diabetes surgery study randomized clinical trial. *JAMA* 2013;309:2240-2249.
74. The Look AHEAD Research Group. Cardiovascular effects of intensive lifestyle intervention in type 2 diabetes. *N Engl J Med* 2013;369:145-154.
75. Khowaja A, Johnson-Rabbett B, Bantle J, Moheet A. Hypoglycemia mediated by paraneoplastic production of insulin like growth factor-2 from a malignant renal solitary fibrous tumor. *BMC Endocrine Disorders* 2014;14:49.
76. The Look AHEAD Research Group. Effect of long-term behavioural weight loss intervention on nephropathy in overweight or obese adults with type 2 diabetes: a

- secondary analysis of the Look AHEAD randomised clinical trial. *Lancet Diabetes Endocrinol* 2014;2:801-809.
77. DCCT/EDIC Research Group. Association between 7 years of intensive treatment of type 1 diabetes and long-term mortality. *JAMA* 2015;313:45-53.
 78. Ikramuddin S, Billington CJ, Lee WJ, Bantle JP, Thomas AJ, Connett JE, Leslie DB, Inabnet WB, Jeffery RW, Keong C, Chuang LM, Sarr MG, Jensen MD, Vella A, Ahmed L, Belani K, Schone JL, Reynolds AE, Bainbridge HA, Wang Q, Korner J. Benefits and risks of roux-en-Y gastric bypass for diabetes: two year outcomes of the diabetes surgery study. *Lancet Diabetes Endocrinol* 2015; 3:413-422.
 79. Bantle AE, Wang Q, Bantle JP. Post-gastric bypass hyperinsulinemic hypoglycemia: fructose is a carbohydrate which can be safely consumed. *J Clin Endocrinol Metab* 2015;100:3097-3102.
 80. Nguyen KT, Billington CJ, Vella A, Wang Qi, Ahmed L, Bantle JP, Bessler M, Connett, JE, Inabnet WB, Thomas A, Ikramuddin S, Korner J. Preserved insulin secretory capacity and weight loss are the predominant predictors of glycemic control in patients with type 2 diabetes randomized to roux-en-Y gastric bypass. *Diabetes* 2015;64:3104-3110.
 81. Ikramuddin S, Korner J, Lee W-J, Bantle JP, Thomas AJ, Connett JE, Leslie DB, Inabnet WB, Wang Q, Jeffery RW, Chong K, Chuang L-M, Jensen MD, Vella A, Ahmed L, Belani K, Olofson AE, Bainbridge HA, Billington CJ. Durability of addition of Roux-en-Y gastric bypass to lifestyle intervention and medical management in achieving primary treatment goals for uncontrolled diabetes in mild to moderate obesity: a randomized clinical trial. *Diabetes Care* 2016;39:1510-1518.
 82. DCCT/EDIC Research Group. Risk factors for cardiovascular disease in type 1 diabetes. *Diabetes* 2016;65:1370-1379.
 83. Buchwald H, Oien DM, Schieber DJ, Bantle JP, Connett JE. Partial ileal bypass affords protection from onset of type 2 diabetes. *Surg Obes Relat Dis* 2017;13:45-52.
 84. Chong K, Ikramuddin S, Lee W, Billington CJ, Bantle JP, Wang Q, Thomas AJ, Connett JE, Leslie DB, Inabnet WB, Jeffery RW, Sarr MG, Jensen MD, Vella A, Ahmed L, Belani K, Schone JL, Olofson AE, Bainbridge HA, Laqua PS, Korner J, Chuang L. National differences in remission of type 2 diabetes mellitus after roux-en-Y gastric bypass surgery - subgroup analysis of 2-year results of the diabetes surgery study comparing Taiwanese with Americans with mild obesity (BMI 30-35 kg/m²). *Obes Surg* 2017;27:1189-1195.
 85. Purnell JQ, Braffett BH, Zinman B, Hokanson JE, Gubitoski-Klug RA, Sivitz W, Bantle JP, Ziegler G, Cleary PA, Brunzell JD and the DCCT/EDIC Research Group. Impact of excessive weight gain on cardiovascular outcomes in type 1 diabetes: Results from the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complication Study (DCCT/EDIC). *Diabetes Care* 2017;40:1756-1762.
 86. Ikramuddin S, Korner J, Lee WJ, Thomas AJ, Connett JE, Bantle JP, Leslie DB, Wang Q, Inabnet WB, Jeffery RW, Chong K, Chuang LM, Jensen MD, Vella A, Ahmed L, Belani K, Billington CW. Lifestyle intervention and medical management with vs without roux-en-Y gastric bypass and control of hemoglobin A1c, LDL cholesterol, and systolic blood pressure at 5 years in the diabetes surgery study. *JAMA* 2018;319:266-278.
 87. Genuth SM, Vlachos H, Brooks MM, Bantle JP, Chaitman BR, Green J, Kelsey SF, King SB, McBane R, Sako EY, Schneider DJ, Steffes M, Frye RL and the BARI 2D Study Group. Bypass Angioplasty Revascularization Investigation 2 Diabetes: A reanalysis focusing on cardiovascular events. *Mayo Clin Proc* 2019;94:2249-2262.
 88. Wadden TA, Chao AM, Bahnson JL, Bantle JP, Blackburn GL, Clark JM, Gaussoin S, Jakicic JM, Johnson KC, Miller GD, Uniack JL, Yanovski SL. End-of-trial health outcomes in Look AHEAD participants who elected to have bariatric surgery. *Obesity* 2019;27:581-590.
 89. Yeh H-C, Bantle JP, Cassidy-Begay M, Blackburn G, Bray GA, Byers T, Clark JM, Coday M, Egan C, Espeland MA, Foreyt JP, Garcia K, Goldman V, Gregg EW, Hazuda HP, Hesson L, Hill JO, Horton ES, Jakicic JM, Jeffery RW, Johnson KC, Kahn SE, Knowler WC, Korytkowski M, Kure A, Lewis CE, Mantzoros C, Meacham M, Montez

- MG, Nathan DM, Pajewski N, Patricio J, Peters A, Pi-Sunyer FX, Pownall H, Ryan DH, Safford M, Sedjo RL, Steinburg H, Vitolins M, Wadden TA, Wagenknecht LE, Wing RR, Wolff AC, Wyatt H, Yanovski SZ. Intensive weight loss intervention and cancer risk in adults with type 2 diabetes: analysis of the Look AHEAD randomized clinical trial. *Obesity* 2020;28:1678-1686.
90. Perkins BA, Bebu I, de Boer IH, Molitch M, Zinman B, Bantle JP, Lorenzi GM, Nathan DM, Lachin JM and the DCCT/EDIC Research Group . Optimal frequency of urinary albumin screening in type 1 diabetes. *Diabetes Care* 2022;45:2943-2949.
 91. Bebu I, Braffett BH, De Boer IH, Aiello LP, Bantle JP, Lorenzi GM, Herman WH, Gubitoski-Klug RA, Perkins BA, Lachin JM, Molitch ME and the DCCT/EDIC Research Group. Relationships between the cumulative incidences of long-term complications in type 1 diabetes mellitus: the DCCT/EDIC Study. *Diabetes Care* 2023;46:361-368.

Book Chapters, Reviews, and Other Publications

1. Bantle JP, Oppenheimer JH. Laboratory assessment of thyroid function. In: Najarian JS, Delaney JP, eds., Endocrine Surgery. New York: Prentice Hall, 1981; pp. 295-307.
2. Bantle JP. Recent advances in the evaluation and treatment of diabetes mellitus. In: Bernstein E, ed., Encyclopaedia Britannica 1985 Medical and Health Annual. Chicago: Encyclopaedia Britannica, Inc., 1984; pp. 235-240.
3. Bantle JP, Oppenheimer JH. Differentiated thyroid carcinoma. In: Hollander VP, ed., Hormonally Responsive Tumors. Orlando, Florida: Academic Press, 1985; pp. 529-540.
4. Bantle JP. Replacement therapy with levothyroxine: Evolving concepts. *Thyroid Today* 1987; 10:1-7.
5. Bantle JP. The dietary treatment of diabetes mellitus. *Med Clin North Am* 1988; 72:1285-1299.
6. Bantle JP. Clinical aspects of sucrose and fructose metabolism. *Diabetes Care* 1989; 12:56-61.
7. Bantle JP. Injection site rotation: the downside. *Practical Diabetology* 1990; 9:1-4.
8. Zeher C, Hansen R, Bantle JP. Reducing blood glucose variability by use of abdominal insulin injection sites. *Diabetes Educ* 1990; 16:474-477.
9. Bantle JP. Thoughts on the dietary treatment of diabetes mellitus. *Diabetes Care* 1992; 15:1821-1823.
10. Wheeler ML, Franz M, Heins J, Schafer R, Holler H, Bohannon B, Bantle JP, Barrier P. Food labeling. *Diabetes Care* 1994; 17:480-487.
11. Franz MJ, Horton ES, Bantle JP, Beebe CA, Brunzell JD, Coulston AM, Henry RR, Hoogwerf BJ, Stacpoole PW. Nutrition principles for the management of diabetes and related complications. *Diabetes Care* 1994;17:490-518.
12. Bantle JP. Current recommendations regarding the dietary treatment of diabetes mellitus. *The Endocrinologist* 1994;4:189-195.
13. Bantle JP. Sugar substitutes, blood glucose levels, and the diabetic diet. *Consultant* 1995;35:1599-1600.
14. Bantle JP. Diabetes mellitus: guide to implementing intensive therapy. *Consultant* 1996; 36:2353-2362.
15. Bantle JP. How to recognize and manage hypoglycemia in diabetes. *Consultant* 1996; 36:2363-2364.
16. Bantle JP. New approaches for the treatment of obesity. *The Bulletin* 1996;40:81-85.
17. Bantle JP, Robertson RP. New approaches to the treatment of type II diabetes mellitus. *Hospital Medicine* 1997;33:19-34.
18. Bantle JP. The adrenal cortex. In: Niewoehner CB, ed., Endocrine Pathophysiology. Madison, Connecticut: Fence Creek, 1998; pp. 61-76.

19. Bantle JP. A physician's perspective on medical nutrition therapy for diabetes. In: Franz MJ, Bantle JP, eds. American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes. Alexandria, VA: American Diabetes Association, 1999; pp. 18-25.
20. Bantle JP. Weight-loss treatments for overweight individuals with diabetes. In: Franz MJ, Bantle JP, eds. American Diabetes Association Guide to Medical Nutrition Therapy for Diabetes. Alexandria, VA: American Diabetes Association, 1999; pp. 69-82.
21. Bantle JP. Diabetes Mellitus. Best Doctors: Information when it matters most; 2000: www.bestdoctors.com.
22. Franz MJ, Bantle JP, Beebe CA, Brunzell JD, Chiasson JL, Garg A, Holzmeister LA, Hoogwerf B, Mayer-Davis E, Mooradian AD, Purnell JQ, Wheeler M. Evidence based nutrition principles and recommendations for the treatment and prevention of diabetes and related complications. *Diabetes Care* 2002;25:148-198.
23. Bantle JP. Impaired fasting glucose: when and how to intervene. *Consultant* 2002; 42:672.
24. Franz MJ, Warshaw H, Daly AE, Green-Pastors J, Arnold MS, Bantle J. Evolution of diabetes medical nutrition therapy. *Postgrad Med* 2003;79:30-35.
25. Bantle JP. Diabetes update 2003. *Audio-Digest Family Practice* 2003;51, issue 36.
26. Bantle JP. Weight management and type 2 diabetes. Medscape Diabetes and Endocrinology 2004;6:www.medscape.com.
27. Bantle JP. Advances in the care of diabetic patients. *Audio-Digest Family Practice* 2004; 52, issue 32.
28. Bantle JP. Diabetes update. *Audio-Digest Family Practice* 2005; 53, issue 44.
29. Bantle JP. Is fructose the optimal low glycemic index sweetener? In: Bantle JP, Slama G, eds., Nutritional Management of Diabetes and Dysmetabolic Syndrome. Basel, Switzerland: Karger, 2006; pp. 83-95.
30. American Diabetes Association (Bantle JP and Wylie-Rosett J, Co-Chairs of writing panel). Nutrition recommendations and interventions for diabetes-2006. *Diabetes Care* 2006;29:2140-2157.
31. Bantle JP, Wylie-Rosett J, Albright AL, Apovian CM, Clark NG, Franz MJ, Hoogwerf BJ, Lichtenstein AH, Mayer-Davis E, Mooradian AD, Wheeler ML. Nutrition recommendations and interventions for diabetes: a position statement of the American Diabetes Association. *Diabetes Care* 2008;31:S61-S78.
32. Buchwald H, Estok R, Fahrenbach K, Banel D, Jensen MD, Poires WJ, Bantle JP, Sledge I. Weight and type 2 diabetes after bariatric surgery: systematic review and meta-analysis. *Am J Med* 2009;122:248-256.
33. Bantle JP. Dietary fructose and metabolic syndrome and diabetes. *J Nutr* 2009;139: 1263S-1268S.
34. Laughlin MR, Bantle JP, Havel PJ, Parks E, Klurfeld DM, Teff K, Maruvada P. Clinical research strategies for fructose metabolism. *Adv Nutr* 2014;5:248-259.

EXHIBIT B

DOCUMENTS CONSIDERED BY DR. JOHN BANTLE

I understand that there may be multiple versions of the materials reviewed and cited herein that have been produced, or may be produced, during the course of this litigation. To the extent that I have cited to or reviewed the documents listed herein, I reserve the right to cite to or consider otherwise identical documents that have been or will be produced during the course of the litigation that bear alternative document numbers or exhibit labels.

To the extent not listed below, documents considered also include all documents cited in my report in this case.

PATENTS

1. U.S. Patent No. 10,335,462 and prosecution history
2. U.S. Patent No. 8,114,833
3. U.S. Patent No. 6,268,343
4. U.S. Patent No. 5,512,549
5. U.S. Patent Pub. No. 2011/0166321
6. U.S. Patent Pub. No. 2007/0010424
7. WO 91/11457
8. WO 03/002136
9. WO 2006/097537
10. WO 2011/058193
11. WO 2011/073328
12. WO 2011/138421

ARTICLES/PUBLICATIONS

1. Banting, *The Internal Secretion of the Pancreas*, 7 J. LAB. CLINICAL MED. 251 (1922)

2. Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)
3. Bhansali, *Historical Overview of Incretin Based Therapies*, 58 J. ASSOC. OF PHYSICIANS OF INDIA 10 (2010)
4. Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)
5. Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003)
6. Drucker, *The Incretin System: Glucagon-Like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors in Type 2 Diabetes*, 368 LANCET 1696 (2006)
7. Drucker, *The Biology of Incretin Hormones*, 3 CELL METABOLISM 153 (2006)
8. 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)
9. HARRISON'S PRINCIPLES OF INTERNAL MED., Chapter 338 (Fauci et al. eds. 17th ed. 2008)
10. Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)
11. 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)
12. 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)
13. 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)
14. 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)

15. Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEMISTRY 4128 (2004)
16. Kundsén, *Liraglutide, A GLP-1 Analogue to Treat Diabetes*, in ANALOGUE-BASED DRUG DISCOVERY II (Fischer & Ganellin eds. 2010)
17. Knudsen, *Liraglutide: The Therapeutic Promise from Animal Models*, 64 INT'L J. CLINICAL PRACTICE 4 (2010)
18. Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REV. ENDOCRINOLOGY 262 (2009)
19. Lund, *Emerging GLP-1 Receptor Agonists*, 16 EXPERT OP. ON EMERGING DRUGS 607 (2011)
20. Marre, *GLP-1 Receptor Agonists Today*, 93 DIABETES RSCH. & CLINICAL PRAC. 317 (2011)
21. Mojsóv, *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)
22. Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)
23. Nielsen, *Pharmacology of Exenatide (Synthetic Exendin-4): A Potential Therapeutic for Improved Glycemic Control of Type 2 Diabetes*, 117 REGUL. PEPTIDES 77 (2004)
24. 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)
25. Tamimi, *Drug Development: From Concept to Marketing!*, 113 NEPHRON CLINICAL PRACTICE c125 (2009)
26. Tasneem, *The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty*, 7(3) PLOS ONE 1 (2012)
27. Vilsbøll, *Glucagon-Like Peptide-1 and Diabetes Treatment*, 21 INTERNATIONAL DIABETES MONITOR 1 (2009)

28. Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364
NEW ENGL. J. MED. 852 (2011)

WEBSITE

1. *Award: ClinicalTrials.gov*, <https://ash.harvard.edu/news/clinicaltrials.gov> (last visited Mar. 15, 2024)
2. *Clinical Trials.gov Background*, CLINICALTRIALS.GOV, <https://clinicaltrials.gov/about-site/about-ctg> (last visited Mar. 15, 2024)
3. *NCT00167115*, CLINICALTRIALS.GOV, <https://www.clinicaltrials.gov/ct2/show/NCT00167115> (last visited Mar. 15, 2024)
4. *NCT01933490*, CLINICALTRIALS.GOV, <https://www.clinicaltrials.gov/ct2/show/NCT01933490> (last visited Mar. 15, 2024)
5. Clinical Trial No. NCT00696657 (Internet Archive)
6. Clinical Trial No. NCT00851773 (Internet Archive)
7. Novo Nordisk Pipeline – Semaglutide (Jan. 27, 2011), http://novonordisk.com:80/science/pipeline/rd_pipeline.asp?showid=7

LABELS

1. Bydureon prescribing information (Jan. 2012)
2. Byetta prescribing information (Oct. 2009)
3. *Victoza*, PHYSICIANS' DESK REFERENCE (65th ed. 2011)

CASE DOCUMENTS

1. Claim Construction Order (July 25, 2023), D.I. 148

DEPOSITIONS

1. Deposition of Christine Jensen and exhibits (Nov. 8, 2023)