UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00724

Patent No. 10,335,462

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

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Full Name of Cited Reference	Abbreviation
U.S. Patent App. Pub. No. 2011/0166321	’321 publication
U.S. Patent App. Pub. No. US2007/0010424	’424 publication
U.S. Patent No. 10,335,462	’462 patent
U.S. Patent App. Pub. No. 2004/0102486	’486 publication
U.S. Patent No. 5,512,549	’549 patent
Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)	Bell
Blonde, *Comparison of Liraglutide Versus Other Incretin-Related Anti-Hyperglycaemic Agents*, 14 (suppl. 2) DIABETES, OBESITY & METABOLISM 20 (2012)	Blonde
Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)	Drab
FDA Guidance for Industry, *Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications* (Apr. 2003)	FDA Exposure Response 2003
Garber, *Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial*, 102 AM. J. MED. 491 (1997)	Garber
Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)	Holst
International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability, 59 Fed. Reg. 55972 (Nov. 9, 1994)	ICH 1994
Kirillova, *Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?*, 7(6) PLOS ONE 1 (2012)	Kirillova

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Knudsen, *Liraglutide: The Therapeutic Promise from Animal Models*, 64(suppl 167) INT J CLIN PRACT 4 (2010)	Knudsen 2010b
Landersdorfer, *Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus*, 47(7) CLIN PHARMACOKINET 417 (2008)	Landersdorfer 2008
Landersdorfer, *Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV*, 73 Br J Clin Pharmacol 391 (2011)	Landersdorfer 2011a
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Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)	Lovshin
Lund, *Emerging GLP-1Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)	Lund
Madsbad, *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
Mojsov, *Insulinotropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLIN. INVEST. 616 (1987)	Mojsov
Møller, *Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test*, 38 J. PHARMACOKINET PHARMACODYN 713 (2011)	Moller

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Full Name of Cited Reference	Abbreviation
Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)	Monami
Murphy, *Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus*, 46 ANN PHARMACOTHER 812 (2012)	Murphy
Clinical Trial No. NCT00696657	NCT657
Clinical Trial No. NCT00851773	NCT773
Rohatagi, *Model-Based Development of a PPARγ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs*, 48 J. CLIN. PHARM. 1420 (2008)	Rohatagi
Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)	Seino
Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)	Shargel
Tamimi, *Drug Development: From Concept to Marketing!*, 113 NEPHRON CLIN PRACT C125 (2009)	Tamimi
Tasneem, *The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty*, 7(3) PLOS ONE 1(2012)	Tasneem
Victoza, PHYSICIANS' DESK REFERENCE (65th ed. 2010)	Victoza label
International Patent App. Pub. No. WO 2011/058193	WO193
International Patent App. Pub. No. WO 2011/073328	WO328
International Patent App. Pub. No. WO 2011/138421	WO421
International Patent App. Pub. No. WO 91/11457	WO457
International Patent App. Pub. No. WO 2006/097537	WO537

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Full Name of Cited Reference	Abbreviation
Yun, *Pharmacokinetic and Pharmacodynamic Modelling of the Effects of Glimepiride on Insulin Secretion and Glucose Lowering in Healthy Humans*, 31 J. CLIN. PHARM. & THER. 469 (2006)	Yun
Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364 NEW ENGL. J. MED. 852 (2011)	Zarin

1. My name is William J. Jusko, Ph.D. I have been retained by counsel for Petitioner Mylan Pharmaceuticals Inc. ("Mylan"). I understand that Mylan is submitting a petition for *inter partes* review ("IPR") of U.S. Patent No. 10,335,462 ("'462 patent," attached as Ex. 1001), which is assigned to Novo Nordisk A/S. It is my understanding that Mylan is requesting that the United States Patent and Trademark Office ("USPTO") cancel all claims of the '462 patent as unpatentable. I submit this expert declaration in support of Mylan's IPR petition for the '462 patent.

I. QUALIFICATIONS AND BACKGROUND

A. EDUCATION AND EXPERIENCE

2. I am a Professor of Pharmaceutical Sciences at the University of Buffalo School of Pharmacy and Pharmaceutical Sciences. My specialty and research focus broadly include Pharmacokinetics, Pharmacodynamics, Pharmacogenomics, and Pharmacometrics.

3. My research interests also include theoretical, basic, and clinical aspects of the pharmacokinetics and pharmacodynamics of various immunosuppressive agents including corticosteroids, as well as drugs used to treat diabetes, inflammation, and cancer.

4. I have characterized the effects of diverse drugs in cells, tissues, animals, and human subjects and have evolved advanced

pharmacokinetic/pharmacodynamic ("PK/PD") models for rapidly acting as well as cascade-type processes. I also have developed mechanism-based pharmacokinetic, pharmacodynamic, and disease progression models and computational methods describing the action of various drugs and utilized mathematical models of drug action to determine optimal dosage regimens for diverse drugs.

5. I have worked as a consultant for the Food and Drug Administration Clinical Pharmacology Advisory Committee, the NIH Pharmacology Study Section, the Council for International Exchange of Scholars, and for many pharmaceutical companies.

6. From 2001 to 2016, I served as chair of the University of Buffalo Department of Pharmaceutical Sciences. More than 100 students and fellows have completed research training under my guidance.

7. I have published more than 670 research articles and serve on the editorial boards of numerous academic journals, including formally being the editor-in-chief for the Journal of Pharmacokinetics and Pharmacodynamics.

8. I received a Bachelor of Pharmacy in 1965 from State University of New York at Buffalo. I remained at State University of New York at Buffalo where I completed my Ph.D. in Pharmaceutical Sciences in 1969.

9. I began my academic career in 1969 as an Assistant Professor of Pharmacology at the Boston University School of Medicine, where I remained for two years.

10. I have been a faculty member at the University of Buffalo since 1972. From 1972 to 1974, I was an Assistant Professor of Pharmaceutics at the University of Buffalo.

11. I remained at the University of Buffalo from 1974 to present, where I transitioned through several roles including as the Director of the Doctor of Pharmacy Program, Vice-Chairman of the Department of Pharmacy, Professor of Pharmaceutical Sciences, Chair of Pharmaceutical Sciences, and Director of the Center of Excellence in Pharmacokinetics and Pharmacodynamics. I am now currently a SUNY Distinguished Professor in Pharmaceutical Sciences.

12. My expertise has been recognized by my peers. I received the 2020 Distinguished Pharmaceutical Scientist Award from the American Association of Pharmaceutical Sciences ("AAPS"). The Distinguished Pharmaceutical Scientist Award is the AAPS's most esteemed honor and is a lifetime achievement that recognizes an individual who has made substantial contributions to the research and advancement of pharmaceutical sciences.

13. I received the 2019 Lewis B. Sheiner Lecturer Award from the International Society of Pharmacometrics ("ISoP"); the 2018 Oscar B. Hunter

Career Award in Therapeutics from the American Society for Clinical Pharmacology and Therapeutics; a coveted MERIT (Method to Extend Research in Time) Award from the National Institutes of Health ("NIH"); and several other awards.

14. I have appreciable experience in studying the pharmaceutical and pharmacological properties of drugs used to treat diabetes. My *curriculum vitae* ("CV") lists at least 31 such publications with 21 involving the study of antidiabetic drugs or the diabetes disease conditions in animal models (diabetic rats) and 10 pertaining to the study of antidiabetic drugs in healthy or diabetic humans. Part of this work was supported by the Pfizer Company when I directed my Department's participation in the UB/Pfizer Strategic Alliance in PK/PD with millions of dollars of support from the company.

15. I am also an inventor on a patent application assigned to SmithKline Beecham Corporation in which I assisted in the development of their antidiabetic drug, Avandia (rosiglitazone) and helped to describe the Exposure/Response (PK/PD) relationships between plasma drug concentrations, lowering of glucose, and lowering of glycated hemoglobin (HbA_{1c}) concentrations in blood in type 2 diabetic patients. *See* Ex. 1078 ('486 publication). This drug was approved by the FDA as the first-in-class known as "insulin sensitizers" that help the uptake of glucose by transporters into tissues. I later helped the Daiichi Sankyo Company in developing rivoglitazone, a drug in the same class with similar effects. *See* Ex. 1044

(Rohatagi). We generated Exposure/Response relationships for a range of doses in these studies.

16. I have particularly relevant experiences pertaining to glucagon-like peptide-1 ("GLP-1")-related mechanisms in diabetes, some of which I discuss in more detail below. I also have considerable experience in designing studies (including dosing studies) and assessing pharmacokinetic and pharmacodynamic data from phase I, II, and III clinical trials. This includes clinical trials for the antidiabetic drugs rosiglitazone, rivoglitazone, pramlintide, vildagliptin, inhaled insulin and others.

17. I am currently a consultant for ReveraGen BioPharma, Inc. advising on dosing in their clinical trials and performing data analyses for their steroid vamorolone in treating adolescent males with Duchenne muscular dystrophy.

18. A copy of my CV, Exhibit 1006, provides a more comprehensive review of my work and describes my qualifications in greater detail, including a list of all publications that I authored during my career.

B. PRIOR TESTIMONY

19. In the past four years, I have testified in the following proceedings:

- *Kellington v. Bayer*, 5:14-CV-00002 (W.D. VA), 2:14-CV-00036-WMA;
- *Hospira Inc. v. Genentech, Inc.*, IPR2017-00805 (PTAB);

- *KVK-Tech, Inc. v. Shire PLC*, IPR2018-00290, IPR2018-00293 (PTAB);
- *Novartis AG v. Apotex Inc.*, Civil Action No. 15-6934 (SRC)(CLW);
- *Tris Pharma, Inc. v. Teva Pharmaceuticals USA, Inc.*, 2-20-cv-05212 (D.N.J.).

C. BASIS FOR OPINIONS AND MATERIALS CONSIDERED

20. A list of the materials I considered, in addition to my experience, education, and training, to provide the opinions contained in this declaration is attached as Exhibit A.

D. RETENTION AND COMPENSATION

21. I have been retained by counsel for Mylan as a technical expert to provide certain of my opinions regarding the '462 patent. I receive $800 per hour for this work. No part of my compensation is dependent upon my opinions given or the outcome of this proceeding.

II. LEGAL STANDARDS

22. In preparing and forming my opinions set forth in this declaration, I have been informed by counsel 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 proceeding.

23. I understand that my opinions regarding unpatentability are presented from the viewpoint of a person of ordinary skill in the art ("POSA" or "skilled artisan") in the field of technology of the patent as of the patent's priority date. In this declaration, my opinions are premised on the perspective of a POSA at the time of the earliest claimed priority date for the '462 patent, which I have been informed for this proceeding is July 1, 2012.[2] *See* Ex. 1001 ('462 patent) at 1.

24. I have been informed that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. I am informed that this

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[1] In performing my analysis and reaching my opinions and conclusions, I have been informed of and have been advised to apply various legal principles relating to unpatentability, which I set forth herein. In setting forth these legal standards, it is not my intention 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 am providing.

[2] To the extent Patent Owner asserts that the claims of the '462 patent are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

"preponderance-of-the-evidence" standard means that the Patent Trial and Appeal Board must find it more likely than not that the claims are unpatentable.

25. I understand that for a patent claim to be unpatentable as anticipated, a prior art reference must disclose each element of the claim expressly and/or inherently as arranged in the claim.

26. Counsel has informed me that the concept of patent obviousness involves four factual inquiries: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and (4) secondary considerations of non-obviousness.

27. It is my understanding from counsel 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. It is my understanding 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.

III. PERSON OF ORDINARY SKILL IN THE ART

28. In my opinion, the following definition of a person of ordinary skill in the art ("POSA" or "skilled artisan") applies to the claims of the '462 patent.

29. A POSA here would have had (1) an M.D., a Pharm. D., or a Ph.D. in pharmacy, chemical engineering, bioengineering, chemistry, or related discipline; (2) at least two years of experience in protein or peptide therapeutic development and/or manufacturing or diabetes treatments; and (3) experience with the development, design, manufacture, formulation, or administration of therapeutic agents, and the literature concerning protein or peptide formulation and design, or diabetes treatments.

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

31. A POSA 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 POSA may collaborate with one or more other POSAs for one or more aspects with which the other POSA may have expertise, experience, and/or

knowledge. Additionally, a POSA could have had a lower level of formal education than what I describe here if the person has a higher degree of experience.

32. As shown by my qualifications provided in my CV and as explained in this declaration, I met the qualifications of a POSA for purposes of the ’462 patent.

33. I understand that Mylan’s formulation expert Dr. Paul Dalby is submitting a declaration with his opinions about why claims 4-10 of the ’462 patent, directed to formulation-related elements, are obvious over the prior art. I defer to Dr. Dalby’s opinion on the formulation-related elements of claims 4-10 of the ’462 patent.

IV. BRIEF SUMMARY OF OPINIONS

34. In my opinion, International Patent Application Publication No. WO 2011/138421 (“WO421”) anticipates claims 1-3 of the ’462 patent.

35. In my opinion, a review article titled “Incretin-Based Therapies for Type 2 Diabetes Mellitus” (“Lovshin”) authored by Julie A. Lovshin and Daniel J. Drucker, which was published in May 2009, anticipates claims 1-3 of the ’462 patent.

36. In my opinion, claims 1-10 of the ’462 patent would have been obvious over WO421 considering U.S. Patent Application Publication No. 2007/0010424 A1 (“’424 Publication”). It is my understanding that Dr. Dalby is offering an opinion that claims 4-10 would have been obvious over WO421 considering the ’424 Publication, and I defer to his opinion for claims 4-10.

37. In my opinion, claims 1-10 of the ’462 patent would have been obvious over International Patent Application Publication No. WO 2006/097537 A2 (“WO537”) considering Lovshin. It is my understanding that Dr. Dalby is offering an opinion that claims 4-10 would have been obvious over WO537 considering Lovshin, and I defer to his opinion for claims 4-10.

38. In my opinion, claims 1-10 of the ’462 patent would have been obvious over Clinical Trial No. NCT00696657 (“NCT657”), Clinical Trial No. NCT00851773 (“NCT773”), and the ’424 Publication. It is my understanding that Dr. Dalby is offering an opinion that claims 4-10 would have been obvious over NCT657, NCT773, and the ’424 Publication, and I defer to his opinion for claims 4-10.

39. Finally, there are no apparent secondary considerations supporting nonobviousness of the claims. I reserve the right to address any secondary considerations put forth by Patent Owner in any later response to this declaration or the petition it accompanies.

V. THE ’462 PATENT [EX. 1001]

A. THE SPECIFICATION AND CLAIMS OF THE ’462 PATENT

40. I have read the ’462 patent, titled “Use of Long-Acting GLP-1 Peptides,” and reviewed the relevant portions of the prosecution history of the ’462 patent (Ex. 1002). The ’462 patent issued from U.S. Patent Application No.

15/656,042 ("'042 Application"), filed July 21, 2017, which is a continuation of U.S. Application No. 14/409,493, filed as PCT/EP2013/063004, filed June 21, 2013, and claims priority to Provisional Application No. 61/708,162, filed October 1, 2012, and Provisional Application No. 61/694,837, filed August 30, 2012, and European patent 12174535, filed July 1, 2012, and European patent 12186781, filed October 1, 2012. Ex. 1001 ('462 patent) at 1. The '462 patent lists Christine Bjoern Jensen as the sole inventor and Novo Nordisk A/S as the Assignee. *Id.*

41. The '462 patent has one independent claim and nine dependent claims.

42. Independent claim 1 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."

43. Claim 2 recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration."

44. Claim 3 recites, "[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection."

45. Claim 4 recites, "[t]he 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."

46. Claim 5 recites, "[t]he method according to claim 4, wherein the solution further comprises propylene glycol and phenol."

47. Claim 6 recites, "[t]he method according to claim 4, wherein the pH is 7.4."

48. Claim 7 recites, "[t]he method according to claim 6, wherein the solution further comprises propylene glycol and phenol."

49. Claim 8 recites, "[t]he method according to claim 4, wherein the phosphate buffer is a sodium dihydrogen phosphate buffer."

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

51. Claim 10 recites, "[t]he method according to claim 9, wherein the pH is 7.4."

B. THE PROSECUTION HISTORY OF THE '462 PATENT

52. The '042 Application that issued as the '462 patent was filed on July 21, 2017 and included independent claim 1, which 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.

See Ex. 1002 (File History) at 8.

53. On July 23, 2018, the Examiner issued a Non-final Office Action, rejecting the claims for, among other rejections, anticipation. Claims 1-10 were rejected as being anticipated by Clinical Trials NCT00696657 (NCT657) as evidenced by Lau, Madsbad as evidenced by the Eperzan assessment report, and Madsbad as evidenced by the Trulicity assessment report, and claims 1-8 and 10 were rejected as anticipated by Kim as evidenced by Bydureon NDA. *See id.* (File History) at 312-15.

54. In response, the Applicant made the following amendments to claim 1:

> 1. (Currently Amended) A method for <u>treating type 2 diabetes, comprising administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof</u>
>
> ~~a) reduction of HbA1c;~~
>
> ~~b) treatment of type 2 diabetes, hyperglycemia, impaired glucose tolerance, or non-insulin dependent diabetes; or~~
>
> ~~c) treatment of obesity, reducing body weight and/or food intake, or inducing satiety;~~
>
> ~~wherein said method comprises administration of a GLP-1 agonist to a subject in need thereof,~~
>
> ~~wherein said GLP-1 agonist~~
>
> ~~i) has a half-life of at least 72 hours;~~
>
> ~~ii) is administered in an amount of at least 0.7 mg per week, such an amount equivalent to at least 0.7 mg semaglutide per week; and~~
>
> ~~iii) is administered once weekly or less often~~.

See id. (File History) at 332.

55. On March 6, 2019, the Examiner issued a Notice of Allowance stating in the Reasons for Allowance:

> The ’657 clinical trial compared semaglutide and liraglutide in treatment of type 2 diabetic patients. The

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

See id. (File History) at 344-45.

VI. CLAIM CONSTRUCTION

56. I understand that claims of a patent subject to *inter partes* review should be construed in accordance with the plain and ordinary meaning of such claim as understood by a POSA in view of the specification of the patent and the prosecution history pertaining to the patent.

57. In my opinion, there are no terms in the claims of the ’462 patent that need construction to resolve the issue of unpatentability of the claims. In my opinion, the claims of the ’462 patent are unpatentable under the plain and ordinary meanings of the claim terms as understood by a POSA.

58. Regarding the preamble of claim 1 of the ’462 patent, “[a] method of treating type 2 diabetes,” in my opinion, the plain and ordinary meaning of that phrase is broad. In view of the specification and prosecution history of the ’462 patent, the plain and ordinary meaning of “[a] method of treating type 2 diabetes”

would be understood by a POSA to broadly encompass administration of semaglutide for the purpose of alleviating or reducing the symptoms and complications associated with type 2 diabetes or otherwise managing the disease without requiring any specified treatment effect.

59. This plain and ordinary meaning is supported by the specification of the ’462 patent, which confirms this meaning of the term “treating” and states:

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

See Ex. 1001 (’462 patent) at 5:20-31.

60. To the extent the preamble is construed as requiring a particular degree of effectiveness, my opinions described in this declaration would remain the same. In my opinion, regardless of any degree of efficacy that may be required of the claims, the prior art provided a POSA with a motivation and reasonable expectation of success of practicing an effective method of treating type 2 diabetes with semaglutide, rendering the claims obvious, or anticipating them.

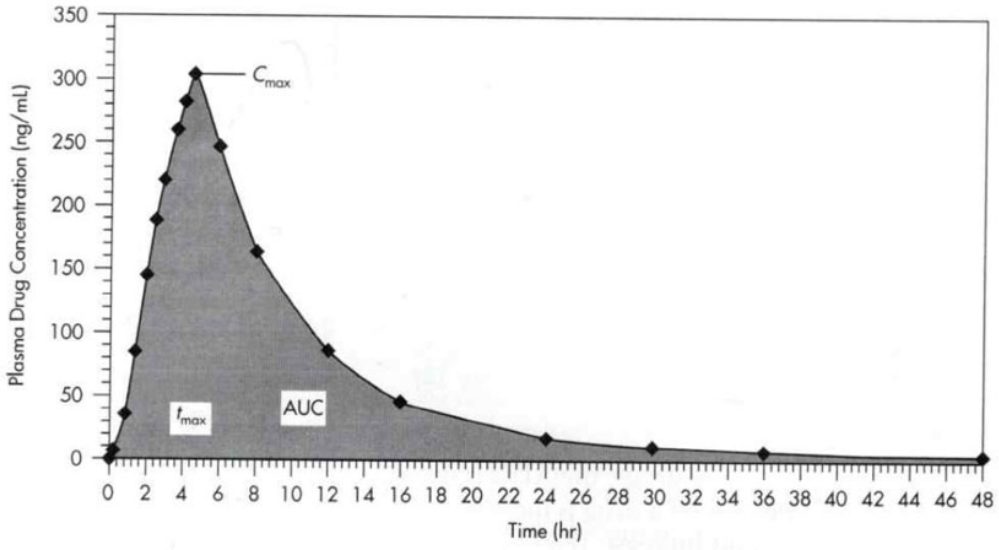
VII. BACKGROUND

A. PHARMACOKINETICS AND PHARMACODYNAMICS

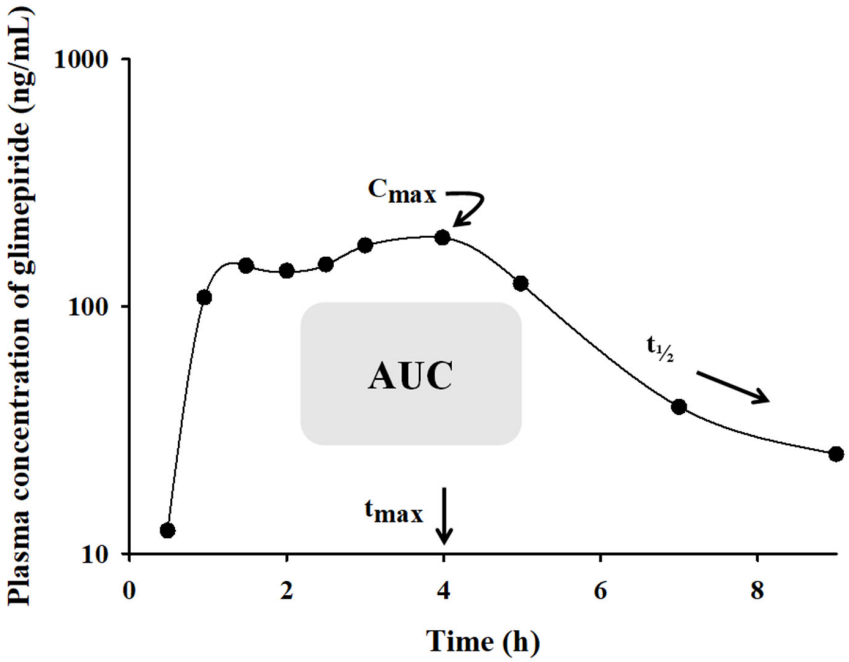
61. Pharmacokinetics ("PK") and pharmacodynamics ("PD") are two branches of pharmacology directed to the study of how a drug interacts with the body. Pharmacokinetics is the description of how the body affects the handling of drugs. Pharmacokinetics describes the time course and factors affecting drug absorption from the site of administration (e.g., gastrointestinal tract, subcutaneous tissue), distribution to various tissues, and elimination by metabolism, renal excretion, and biliary excretion. *See* Ex. 1045 (Shargel) at 15. Characterizing the distribution and elimination of a drug is an important prerequisite for determination or modification of dosing regimens for patients. *Id*. The study of pharmacokinetics involves both experimental approaches, e.g., analytical methods for the measurement of drugs and metabolites in animals and humans, and theoretical approaches, development of pharmacokinetic models that quantitate and/or predict drug disposition after drug administration. *Id.*

62. The simplest expression of pharmacokinetics is the "exposure" of the drug, namely the relationship between plasma (blood) concentrations and time where parameters such as C_{max} (maximum concentration), t_{max} (time of maximum concentration), AUC (Area Under the Concentration-Time Curve), and $t_{1/2}$ (half-life)

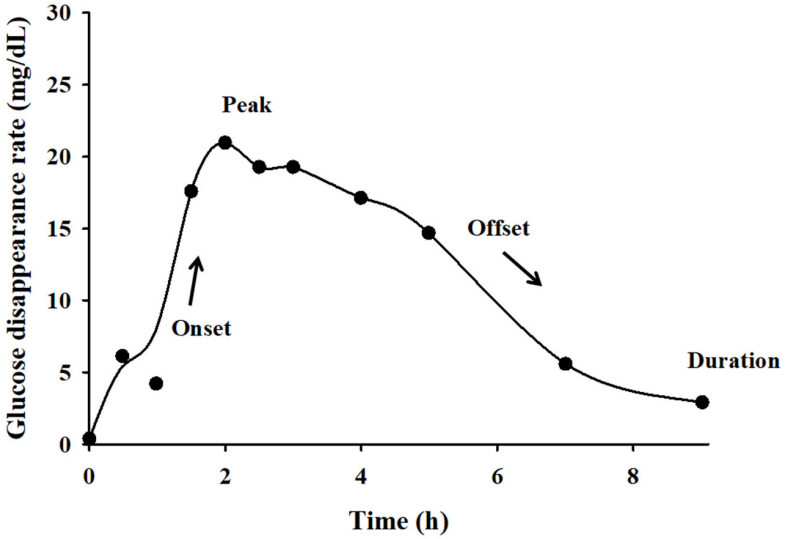
are described and measured, such as the graph set forth below. *Id.* at 40, Figure 15-1.



63. For example, the graph shown below is adapted from Figure 2 of Yun, showing such properties for the antidiabetic drug glimepiride (Amaryl®) in healthy human subjects after administration of a single 2 mg oral dose. *See* Ex. 1046 (Yun) at Fig 2.



64. Pharmacodynamics is the description of how the drug affects the body, and refers to the relationship between the drug concentration in blood or at the site of action and the pharmacologic response. *See* Ex. 1045 (Shargel) at 16. It describes the time course and factors affecting the onset, peak, and duration of drug responses after single and multiple doses of a drug. While such responses are determined by many factors and exhibit many time courses, the simplest of graphs would show these phases in tandem with a pharmacokinetic profile (i.e., PK/PD), such as shown above. The graph below demonstrating these properties is adapted from Figure 6 of Yun, and shows the effects of administration of a single 2 mg dose of glimepiride on utilization of glucose in healthy human subjects. *See* Ex. 1046 (Yun) at Fig 6.



B. DRUG DEVELOPMENT - CLINICAL TRIAL DESIGN

65. The process of designing a drug is long-term and expensive, involving different phases of drug development, starting with discovery, preclinical studies including basic research, laboratory experiments and animal studies before moving to human clinical studies (phase I-IV studies). *See* Ex. 1047 (Tamimi) at 1-2, Fig. 1 (see schematic below reproduced from Fig. 1 of Tamimi).

66. Before a drug can be tested in humans, the United States Food and Drug Administration (FDA) and other regulatory agencies require that preclinical studies be performed to predict that the drug can be safely given to humans. *See* Ex. 1066 (Knudsen 2010b) at 1; Ex. 1047 (Tamimi) at 3. Preclinical studies involve obtaining

functional biochemical properties such as receptor binding and pharmacokinetic testing *in vitro* and pharmacodynamic and pharmacokinetic testing *in vitro* and *in vivo* of the drug, including studies in animal models to explore the drug's mechanistic effects on different tissues and organs. *See* Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1. Next, a suitable formulation is developed for the drug and the drug is "progressed through the required toxicology testing (including genotoxicity, safety pharmacology in all biological systems, single and multiple dose toxicity and toxicokinetic studies) to enable the first in human and subsequent clinical studies." Ex. 1047 (Tamimi) at 3; *see* Ex. 1084 (ICH 2001) at 5-8 ("The effects of a test substance on the functions listed in the safety pharmacology core battery should be investigated prior to first administration in humans."). Prerequisites for filing a drug approval request include reproductive toxicology in male and female animals and long-term carcinogenicity testing. *Id.* Thus, by the time a drug reaches the phase to be evaluated in humans, an extensive body of data will have been generated to understand its therapeutic potential and minimize risks. *See* Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1.

67. After the preclinical testing is satisfied, there are four phases for evaluating new drugs, phases I-IV. Phase I studies include a small number of healthy subjects, with the purpose to evaluate the safety, tolerability, pharmacodynamic and pharmacokinetic effects of the drug. *See* Ex. 1047 (Tamimi) at 3. A range of doses

are investigated in a phase I study, including a minimum dose extending to maximum tolerated dosages. All phase I-IV studies require approval from ethics committees and the relevant regulatory agency. *Id.* Additional phase I studies can be conducted throughout any of the other phases of development. *Id.*

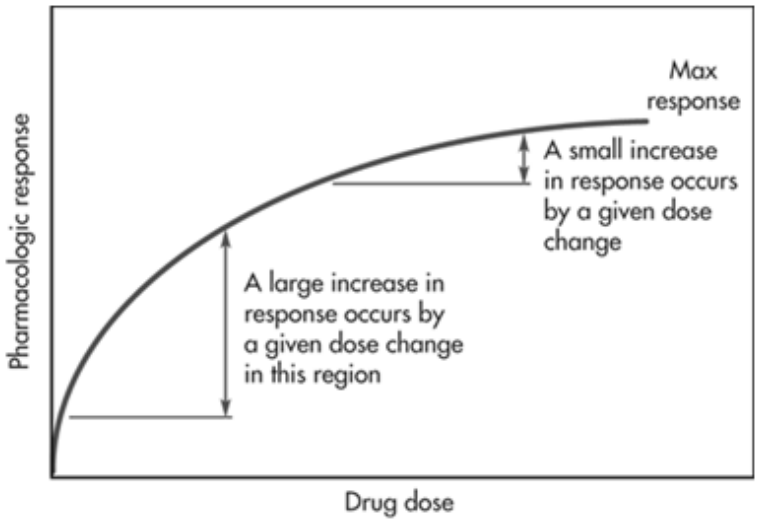
68. Following establishment of the drug's safety, pharmacokinetics, and dose selection in healthy volunteers in a phase I study, the efficacy and safety of the drug is next investigated in persons who have the disease/condition the drug is intended to treat in one or more phase II studies. Ex. 1047 (Tamimi) at 4. Phase II studies can be divided into phase IIa and phase IIb, or can be combined into one large study, which can include several hundred patients. *Id.* Phase II studies define the minimally effective or non-effective dose and assist in selecting the optimal doses, based on clinical efficacy and safety, to pursue in the much larger phase III study. *Id.* A range of doses from suboptimal to maximally effective doses are typically investigated in the phase II study to determine optimal doses, which are doses with an acceptable balance of beneficial effects and undesired effects. *Id.*; *see also, e.g.,* Ex. 1049 (ICH 1994) at 1-2 ("What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects."), 4 ("It is important to choose as

wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences."), 6 ("Depending on circumstances (the disease, the drug's toxicity), the starting dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose."); Ex. 1048 (FDA Exposure Response 2003) at 5, 7 ("The dose-response study is a particularly informative design, allowing observations of benefits and risks at different doses and therefore providing an ability to weigh the benefits and risks when choosing doses. The dose-response study can help ensure that excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity.").

69. Both the FDA and other international regulatory bodies (including from Europe and Japan) encourage the determination of "Exposure/Response" during the development of new drugs. *See* Ex. 1048 (FDA Exposure Response 2003) at 5 ("Exposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known."); Ex. 1049 (ICH 1994) at 1-2, 4, 6. This involves the assessment of both pharmacokinetics and pharmacodynamics over a range of doses in seeking to understand what doses are optimal and the rates of undesired effects in human subjects and how to best use the drug in patients. Ex. 1047 (Tamimi) at 3-4; Ex.

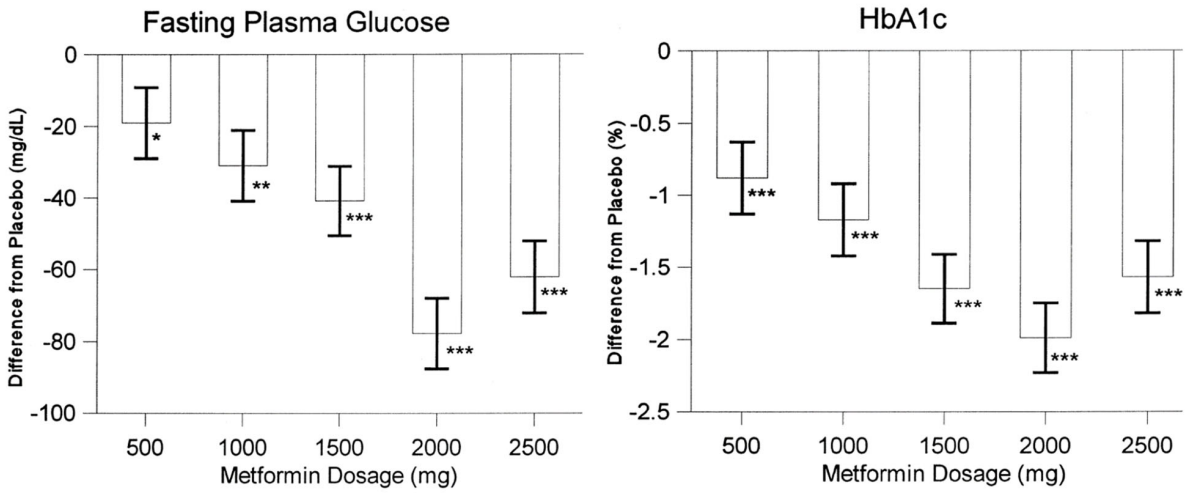
1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6. The results of such studies in the phase I or phase II assessment of PK/PD often yield pharmacodynamic parameters such as the E_{max} (maximum effect of the drug) and EC_{50} (drug concentration producing one-half of the E_{max}). *See* Ex. 1045 (Shargel) at 82, Figs. 19-1, 19-2.

70. The pharmacologic effect of a drug depends on the dose and the pharmacokinetics of the drug. *See* Ex. 1045 (Shargel) at 81. As the dose of the drug increases, the concentration at the receptor or target site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic curve with maximum pharmacologic effect (E_{max}) at the plateau on the dose-response curve, as shown in the figure below (reproduced from Figure 19-1 of Shargel). *Id.* at 81-82.



71. Typically, the optimal dose is often the smallest dose providing the near maximal treatment effect (i.e., the lowest dose near or on the plateau) because higher doses usually result in higher adverse event rates. To best understand the Exposure/Response of a drug, phase II studies typically investigate a range of doses including lower doses and higher doses that are predicted to be on the dose-response curve plateau. *See* Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6.

72. An example of a phase II dose-response study in which the efficacy of a range of dosages of a drug were investigated was the phase II double-blind, placebo contolled, dose response trial testing various doses of metformin as compared with placebo in patients with type 2 diabetes. *See* Ex. 1050 (Garber) at 1-2. The dose-response bar graphs from this study provided below illustrate the responses (consisting of lowering of fasting plasma glucose and glycated hemoglobin, HbA_{1c}) versus a range of doses of metformin, which is typical for a phase II dose-response study. *See id.* at 5, Fig. 1.



73. As shown in the bar graphs above, the metformin doses administered to patients with type 2 diabetes ranged from low doses (500 mg) to much higher doses (2000 mg and 2500 mg), with the maximum efficacy of metformin observed at 2000 mg, not 2500 mg. *See id.* at 5, Fig. 1. The highest dose of metformin administered, 2500 mg, would fall well onto the plateau of the dose-response curve.

74. If the drug shows promising efficacy in a successful phase II study, then larger phase III studies can be performed to confirm the clinical doses, timing, and frequency prior to registration. Ex. 1047 (Tamimi) at 4. Typically, a minimum of two phase III studies are performed, involving up to several thousand patients. *Id.* Finally, once successful phase III studies are completed, the data are compiled and submitted to the appropriate regulatory agency. *Id.* at 5. Phase IV studies include post-marketing or safety surveillance trials. *Id.* at 5-6.

C. PHARMACOKINETICS AND PHARMACODYNAMICS RELATED TO GLP-1 AND SEMAGLUTIDE

75. Type 1 diabetes is characterized by the body's inability to produce insulin, whereas type 2 diabetes involves a genetic susceptability resulting in insulin deficiency and an excessive glucagon secretion. Ex. 1051 (Landersdorfer 2008) at 2; Ex. 1052 (Madsbad) at 1. The are a diversity of drugs, hormones, and mediators that can affect glucose, which can be used or modulated to treat diabetes. In 2008, I published a review of mathematical (PK/PD) methods and models for several such anti-diabetic drug effects. *See* Ex. 1051 (Landersdorfer 2008).

1. GLP-1

76. In the early 1980s, two peptides, glucagon-like peptide 1 ("GLP-1") and glucagon-like peptide 2 ("GLP-2"), related to the hormone glucagon were identified. *See generally* Ex. 1019 (Bell). GLP-1 is a 30 amino acid peptide produced and secreted from intestinal enteroendocrine L cells after meal ingestion. Ex. 1035 (Lund) at 1. GLP-1 binds to GLP-1 receptors (GLP-1R) expressed on pancreatic beta cells resulting in the stimulation of insulin secretion, suppression of glucagon secretion, slowing of gastric emptying, and (likely by binding to GLP-1R in the brain) inducing a feeling of satiety thereby reducing food intake. *Id.* at 1-2. Owing to these benefits, pharmacological strategies based on GLP-1 based therapies were pursued for the treatment of type 2 diabetes. *Id.* at 2. I supervised the mathematical analysis of GLP-1 profiles obtained by Novo Nordisk from type 2

diabetic subjects after an oral glucose tolerance test and developed a PK/PD model to describe the production and loss of GLP-1 in plasma over 4 hours. *See* Ex. 1053 (Moller).

77. GLP-1 has a short half-life owing to rapid degradation by the enzyme dipeptidyl peptidase IV (DPP-4) found in plasma and tissues. *See* Ex. 1012 (Lovshin) at 2. One method of treating diabetes was to administer inhibitors of DPP-4 (known as incretin enhancers) and thereby extend the action of naturally secreted GLP-1. Before the earliest claimed priority date, there were at least six known DPP-4 inhibitors, including sitagliptin, vildagliptin, alogliptin, saxagliptin, linagliptin, and dutogliptin. *See* Ex. 1012 (Lovshin) at 2, Table 1 (listing DPP-4 inhibitors). I assisted in developing a PK/PD Exposure/Response model for vildaglipin (Galvus®), used to assess the pharmacokinetics and actions of vildagliptin at different doses. *See* Ex. 1054 (Landersdorfer 2011a); Ex. 1055 (Landersdorfer 2011b).

2. GLP-1 derivatives

78. Further studies related to GLP-1 found that the body naturally synthesizes truncated forms of the GLP-1 peptide, including GLP-1 (7-37). *See*, *e.g.*, Ex. 1036 (Mojsov); Ex. 1027 (Holst). In addition to inhibiting the secretion of glucagon, a hormone that raises blood glucose, GLP-1 (7-37) was found to have an insulinotropic (stimulating insulin secretion) effect. Ex. 1036 (Mojsov) at 1-3; Ex. 1027 (Holst) at 4-6. In the early and mid-1990s, GLP-1 derivatives (including

derivatives of GLP-1 (7-37)) were being developed that possessed improved pharmacological properties. *See*, *e.g.*, Ex. 1017 ('549 patent) at Abstract, 1:9-11, 2:27-32, 3:9-11, 25-30; Ex. 1042 (WO457) at 4:24-29, 5:2-7. Thus, GLP-1 and certain of its truncated forms (e.g., GLP-1 (7-37)) were known by skilled artisans to be potential therapeutic agents for the treatment of type 2 diabetes, owing to their ability to stimulate insulin, inhibit glucagon, and ultimately lower blood glucose levels.

79. Exendin-4 is a GLP-1 analog, isolated from the venom of Gila monsters, that shares 53% sequence identity with GLP-1 and binds to GLP-1 receptors (GLP-1Rs) but has the advantage of greater stability against DPP-4 and thus prolonged pharmacokinetics. *See* Ex. 1032 (Knudsen 2004) at 2-3. The figure below (reproduced from Figure 3 of Knudsen 2004) summarizes the understanding gained from GLP-1 and exendin-4 studies, including the DPP-IV cleavage site and amino acid residues essential for binding the GLP-1 receptor. Ex. 1032 (Knudsen 2004) at 3, Fig. 3. As shown in the figure below, the amino acids essential for binding are His7, Gly10, Phe12, Thr13, Asp15, Phe28, Ile29, and Val33. Ex. 1032 (Knudsen 2004) at 3, Fig. 3.

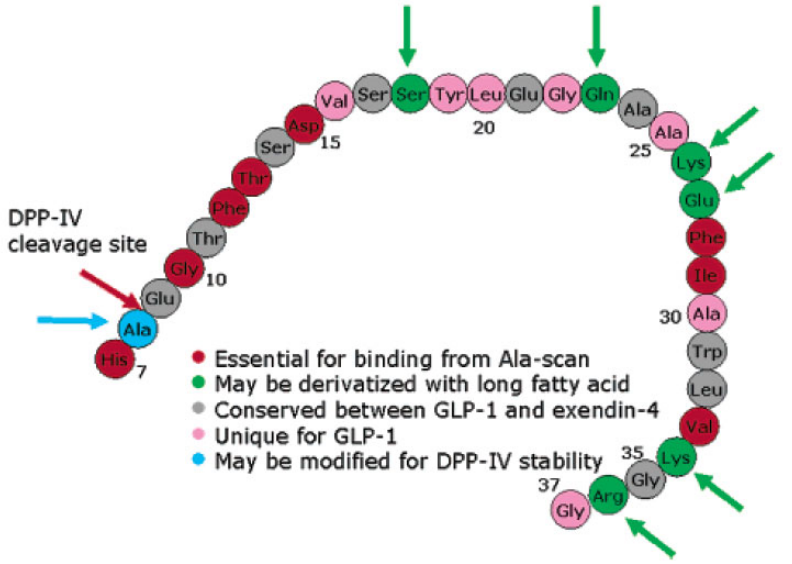


Figure 3. SAR figure of GLP-1. All sites essential for binding from Ala-scan are also conserved between GLP-1 and exendin-4. Sites that are possible to modify with fatty acids are only color-coded as such. They are all unique for GLP-1 at the same time.

80. Further research into the use of GLP-1 and its derivatives ultimately resulted in FDA approval of several GLP-1R agonists such as exenatide and liraglutide to treat type 2 diabetes. *See* 1012 (Lovshin) at 2; Ex. 1039 (Victoza label). Exenatide is synthetic exendin-4, which was approved by the FDA in 2005 for the treatment of type 2 diabetes. *See* Ex. 1012 (Lovshin) at 2. Exenatide initially was administered subcutanously twice daily for treatment of type 2 diabetes, but was subsequently formulated for slow release so that it needed to only be administered once weekly. *Id.* As disclosed in Lovshin, "the success of exenatide accelerated the development of new GLP-1R agonists with pharmacokinetic properties optimized for once-daily or once-weekly administration." *Id.* at 3.

81. As disclosed in the prior art, a benefit of once weekly dosing for GLP-1 receptor agonists in development 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)." Lund (Ex. 1035) at 5. Knudsen disclosed, "[n]ausea may best be avoided by a long half-life because a long half-life gives the smallest needed excursions in plasma concentrations." Ex. 1032 (Knudsen 2004) at 4.

a. Liraglutide

82. Liraglutide is "an analog of human GLP-1 and acts as a GLP-1 receptor agonist," and is the active ingredient in Victoza®. Ex. 1039 (Victoza label) at 5. Liraglutide "is made by attaching a C-16 fatty acid (palmitic acid) with a glutamic acid spacer on [a] lysine residue at position 26 of the peptide precursor." *Id.* at 5. The amino acid sequence of liraglutide is shown below:

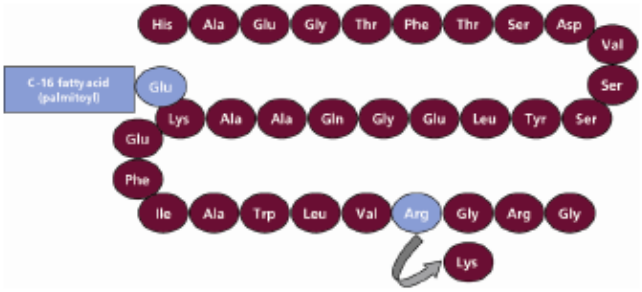


Figure 1 Structural Formula of liraglutide

Id.[3]

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

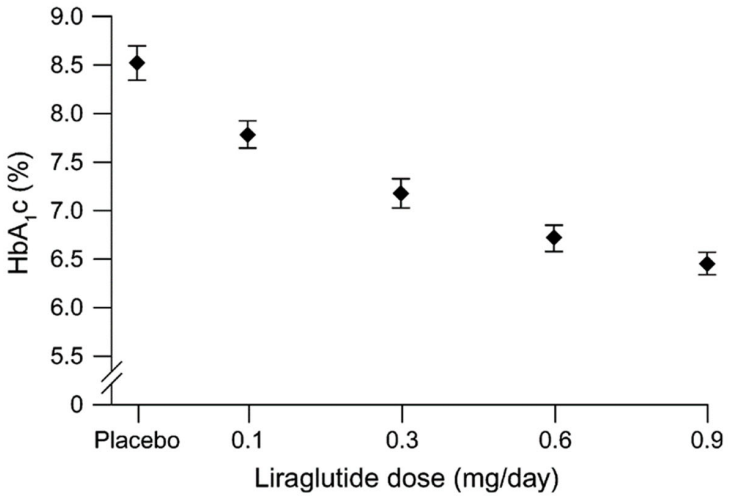
HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG

84. The amino acid residues shown to be essential in GLP-1 for GLP-1 receptor binding are also present in liraglutide. *See* Ex. 1032 (Knudsen 2004) at 3, Fig. 3.

85. Before the earliest priority date, skilled artisans would have known that liraglutide was the subject of numerous clinical studies and publications describing its effectiveness and was studied alone or alongside other diabetes therapies. *See, e.g.*, Ex. 1058 (Blonde); Ex. 1035 (Lund); Ex. 1052 (Madsbad); Ex. 1059 (Murphy). The development of liraglutide included studies of the pharmacokinetics and glucose lowering in animal models and then Phase 1 and Phase 2 dose-ranging studies in healthy subjects and type 2 diabetic patients. *See* Ex. 1066 (Knudsen 2010b); Ex. 1052 (Madsbad). Liraglutide exhibits consistent dose/response profiles for lowering HbA_{1c} as might be expected for any agent that functions as a GLP-1 agonist. The

[3] This figure appears in Exhibit 1039, however, for purposes of readability this figure is from the electronic version of the Victoza label found at Drugs@FDA website (https://www.accessdata.fda.gov/drugsatfda_docs/label/2022/022341s037s038lbl.pdf (last visited Mar. 14, 2023).

graph shown below from Figure 1 of Seino provides one of the earliest Dose/Response profiles published for liraglutide showing lowering of HbA_{1c} after 14 weeks of once-daily treatment of type 2 diabetic patients. *See* Ex. 1038 (Seino) at 4, Fig. 1.



86. The narrow error bars (representing the standard error) indicate that variability was modest at each dose level and that higher doses produced stronger effects than lower doses, reflecting a clear dose-response relationship for HbA_{1c}. *See id.* at 6 ("A clear dose response relationship for HbA_{1c} was shown in this study."). Moreover, as shown above, liraglutide showed the classic sigmoidal dose/response profile for lowering HbA_{1c}. As reported in Seino, "[a]ll doses of liraglutide tested showed a degree of efficacy." *Id.* While it was not clear whether a plateau was reached, the progression of increasing responses with higher doses offered confidence that the properties of this GLP-1 agonist within the incretin system were

well-understood. For example, there was no loss of efficacy during chronic exposure from possible antibodies to liraglutide. *Id.* at 4. By the time that the Victoza label (Ex. 1039) was approved, liraglutide had been studied at higher doses than 0.9 mg/day, such as 1.2 mg/day and 1.8 mg/day. Ex. 1039 (Victoza label) at 6-7, Table 4.

87. Liraglutide was approved in 2010 as Victoza® "as an adjunct to diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus." Ex. 1039 (Victoza label) at 2. Drab disclosed that "as with exenatide, the most common adverse effect of liraglutide is nausea." Ex. 1022 (Drab) at 10. Drab disclosed that during the phase III trials, "the frequency of nausea with liraglutide ranged from 10.5% when combined with a sulfonylurea to 40% with a thiazolidinedione." *Id.* "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.*

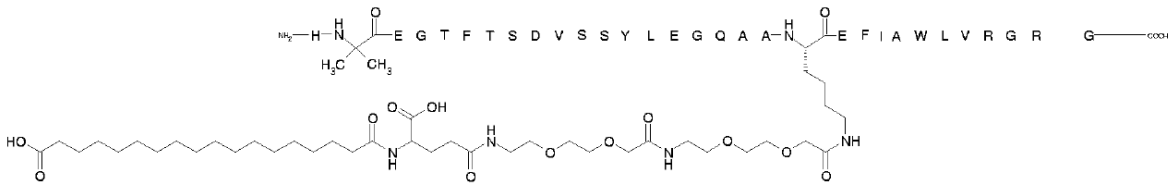
88. As disclosed on the Victoza label, liraglutide was to be subcutaneously "[a]dminister[ed] once daily at any time of day, independently of meals." *Id.* After one week of dosing at 0.6 mg daily, the dose of Victoza® was increased to 1.2 mg daily for long-term treatment, an amount that could be "increased to 1.8 mg" if the lower dose "[did] not result in acceptable glycemic control." *Id.* This demonstrates that 1.2 mg was not the maximum effective or maximum tolerated dose, and that a

reasonably large increase (50%) produced a greater effect with acceptable tolerance. *See id.* at Table 4, Fig. 3.

b. Semaglutide

89. Prior to the earliest alleged priority date, skilled artisans were investigating another GLP-1 derivative receptor agonist, semaglutide, which was also sometimes referred to as NN9535. *See* Ex. 1060 (WO193) at 35:18 ("semaglutide/NN9535 (Novo Nordisk)"); *see also* Ex. 1035 (Lund) at 4, Table 1 ("Semaglutide (NN9535) Novo Nordisk"); Ex. 1012 (Lovshin) at 2, Table 1.

90. Example 4 of WO537 disclosed the structure of semaglutide (N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg 34]GLP-1-(7-37)peptide):



Ex. 1015 (WO537) at 48:4-22 (Example 4); *see also* Ex. 1061 ('321 publication) at [0010] ("WO 06/097537 discloses a number of GLP-1 derivatives including semaglutide (Example 4), a mono-acylated GLP-1 derivative for once weekly administration which is under development by Novo Nordisk A/S.").

91. Thus, a skilled artisan would have known the primary amino acid sequence of semaglutide. In single letter abbreviation, that amino acid sequence is:

H[A]EGTFTSDVSSYLEGQAAKEFIAWLVRGRG

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

92. Like liraglutide, the amino acid residues shown to be essential in GLP-1 for GLP-1 receptor binding are also present in semaglutide. *See* Ex. 1032 (Knudsen 2004) at 3, Fig. 3.

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

D. SEMAGLUTIDE CLINICAL TRIALS

94. Before the priority date, it was well-known that semaglutide was a once weekly GLP-1 receptor agonist used to treat diabetes. *See* Ex. 1035 (Lund) at Fig. 1; Ex. 1012 (Lovshin) at 2, Table 1; Ex. 1015 (WO537) at 23:24-24:3; 48:4-22; Ex. 1011 (WO421) at 44:9-10, claim 17. Skilled artisans would have known semaglutide was being investigated in in phase I and II clinical studies. *See* Ex. 1035 (Lund) at Fig. 1; Ex. 1012 (Lovshin) at 2, Table 1. For example, Lund disclosed that multiple trials involving semaglutide were completed or in process:

> 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).

Ex. 1035 (Lund) at 7-8.

95. A skilled artisan would have been aware that the dose range being investigated in clinical trials for semaglutide was 0.1-1.6 mg once weekly. Ex. 1012 (Lovshin) at 2, Table 1; Ex. 1011 (WO421) at 44:13. Indeed, the phase II study, NCT00696657 ("NCT657"), titled "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," and sponsored by Novo Nordisk, was investigating such doses. Ex. 1013 (NCT657) at 15-16. NCT657 was a 12-week study that began in June 2008 and was completed in February 2009. *Id.* at 15.

96. The "Purpose" section of NCT657 disclosed:

> This trial was conducted in Europe, Asia and Africa. Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW - 1.6 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

Id. at 15.

97. NCT657 had six Experimental arms (A-F), which included once weekly subcutaneous (s.c.) injections of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration) semaglutide. *Id.* at 15-16. NCT657 also had six Placebo Comparator arms (G1-G6), which included once weekly subcutaneous injections of 0.1 mg, 0.2 mg, 0.4 mg, and 0.8 mg, 0.8 mg (with titration), and 1.6 mg (with titration) placebo and two Experimental arms (H and I), which included once daily subcutaneous injections of 1.2 mg and 1.8 mg liraglutide, respectively. *Id.* at 16.

98. A skilled artisan would have also been aware of the Phase I study, NCT00851773 ("NCT773"), titled "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," also sponsored by Novo Nordisk. Ex. 1014 (NCT773) at 7; Ex. 1035 (Lund) at 7-8. The phase I NCT773 was an 8-week study that began in February 2009, the same month the phase II NCT657 was completed, and was completed in October 2009. Ex. 1014 (NCT773) at 7.

99. The "Purpose" section of NCT773 disclosed:

> 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.

100. NCT773 had five Experimental arms (A-E), which included once weekly subcutaneous injections of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg (with titration), and 1.2 mg (with titration). *Id.* at 7-8. NCT773 also had five Placebo Comparator arms (F1-F5), which included once weekly subcutaneous injections of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg (with titration), and 1.2 mg (with titration) placebo. *Id.* at 7-8.

101. Based on these disclosures, skilled artisans would have been aware that the dosing regimen between the earlier phase II NCT657 study and the later phase I

NCT773 study were different. Whereas the highest dose tested in the phase II NCT657 study was 1.6 mg semaglutide, the highest dose tested in the NCT773 study was only 1.2 mg semaglutide.

102. Thus, before the earliest claimed priority date of the ’462 patent, skilled artisans would have been aware that Novo Nordisk was actively investigating once weekly doses of semaglutide and were homing in on the optimal doses of semaglutide, to treat diabetes.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

103. Set forth below are prior art references supporting my expert opinions on unpatentability of claims 1-10 of the ’462 patent. All the references I cite in this document would have been known, and publicly available, to a POSA as of the relevant priority date.

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

for just one or several of its teachings, I reserve the right to rely on that reference for any other aspect of its teaching.

105. 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 in this declaration, I rely generally on the knowledge of a POSA at the time of invention, including, without limitation, the knowledge described generally in this declaration (i.e., without referring to a specific document).

A. WO421 [Ex. 1011]

106. International Patent Application Publication No. WO 2011/138421 ("WO421") titled "Combination Therapy" was published on November 10, 2011, before the earliest claimed priority date of the '462 patent. Ex. 1011 (WO421) at 1. The international application that published as WO421, PCT/EP2011/057256, was filed on May 5, 2011. WO421 claims priority to two European patent applications, 10162036.7, filed May 5, 2010 and 11155154.5, filed February 21, 2011. *Id.* Boehringer Ingelheim International GMBH is listed as the applicant and Thomas Klein, Rolf Grempler, and Michael Mark are listed as inventors. *Id.*

107. WO421 disclosed:

> The present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2

> diabetes mellitus, obesity and/or conditions related thereto (e.g. diabetic complications) comprising the combined administration of a GLP-1 receptor agonist (e.g. exogenous GLP-1 or a GLP-1 analogue) and a certain DPP-4 inhibitor, to pharmaceutical compositions and combinations comprising such active components, and to certain therapeutic uses thereof.

Id. at 2:4-9.

108. WO421 also disclosed, "[n]on-oral (typically injected) antidiabetic drugs conventionally used in therapy (such as e.g. first- or second-line, and/or mono- or (initial or add-on) combination therapy) include, without being restricted thereto, GLP-1 or GLP-1 analogues, and insulin or insulin analogues." *Id.* at 6:19-21.

109. WO421 disclosed "[p]referred examples of GLP-1 receptor agonists (GLP-1 analogues) of this invention are exenatide, exenatide LAR [i.e., long-acting release formulation], liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide." *Id.* at 34:20-22.

110. Claim 17 of WO421 recites:

> A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, semaglutide, albiglutide, lixisenatide and dulaglutide, for use in a method of treating type 2 diabetes, obesity or both, said method comprising administration (e.g. separate,

> sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Id. at 65:27-31.

111. WO421 disclosed "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)" and "[l]iraglutide is administered once daily by subcutaneous injection (Victoza, 0.5-3 mg, particularly 0.5 mg to 2 mg, specific dosage strengths are 0.6 mg, 0.9 mg, 1.2 mg or 1.8 mg)." *Id.* at 44:9-10, 13.

B. LOVSHIN [EX. 1012]

112. "Incretin-Based Therapies for Type 2 Diabetes Mellitus" ("Lovshin") is the title of a review article authored by Julie A. Lovshin and Daniel J. Drucker. Lovshin was published in 2009, before the earliest claimed priority date of the '462 patent. Ex. 1012 (Lovshin) at 1.

113. Lovshin disclosed:

> 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.

Id. at 1.

114. Lovshin stated "[h]erein, we review the data from clinical trials that have assessed GLP-1R agonists and DPP-4 inhibitors (Table 1) and highlight emerging incretin-based therapies that are in the late stages of clinical testing." *Id*. Table 1 of Lovshin disclosed that NN9535, also known by skilled artisans as semaglutide,[4] was being investigated at a dose of "0.1-1.6 mg once weekly." *Id.* at 2, Table 1 (reproduced below).

[4] *See* Ex. 1060 (WO193) at 35:18 ("semaglutide/NN9535 (Novo Nordisk)"); *see also* Ex. 1035 (Lund) at 4, Table 1 ("Semaglutide (NN9535) Novo Nordisk").

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.

Id. at 2, Table 1.

115. Lovshin also disclosed, "multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1)." *Id.* at 5.

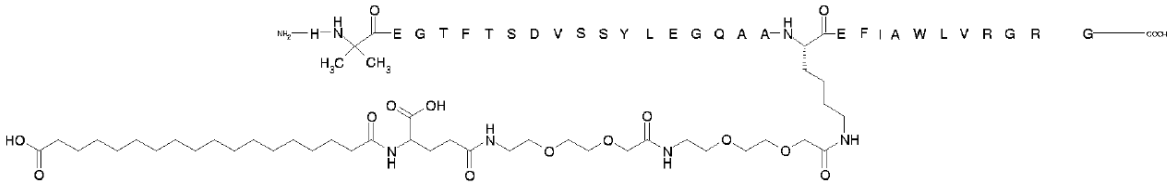
C. WO537 [Ex. 1015]

116. International Patent Application Publication No. WO 2006/097537 A2 ("WO537") is titled "Acylated GLP-1 Compounds," and was published on

September 21, 2006, before the earliest claimed priority date of the ’462 patent. Ex. 1015 (WO537) at 1. Novo Nordisk A/S is listed as the applicant of WO537 and Jesper Lau, Florencio Zaragoza Dörwald, Henrik Stephensen, Paw Bloch, Thomas Kruse Hansen, and Kjeld Madsen are listed as inventors. *Id.*

117. WO537 disclosed that “[t]he invention relates to the field of therapeutic peptides, i.e. to new protracted GLP-1 compounds.” *Id.* at 2:5-6.

118. Example 4 of WO537 disclosed the structure of semaglutide (N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg 34]GLP-1-(7-37)peptide):



Id. at 48:4-8. Claim 28 of WO537 also disclosed semaglutide. *Id.* at 73:17-75:10.

119. WO537 disclosed that semaglutide could be used in “a medicament for the treatment or prevention of hyperglycemia, type 2 diabetes, impaired glucose tolerance, type 1 diabetes, [or] obesity,” or “for delaying or preventing disease progression in type 2 diabetes.” *Id.* at 23:24-24:3.

120. WO537 disclosed that the disclosed formulations could be administered parenterally, such as by subcutaneous injection. *Id.* at 35:15-16 (“Parenteral

administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.”).

D. SEMAGLUTIDE CLINICAL TRIALS

1. NCT657 [Ex. 1013]

121. Clinical Trial No. NCT00696657 (“NCT657”) is titled “A Randomised Controlled Clinical Trial in Type 2 Diabetes Comparing Semaglutide to Placebo and Liraglutide” and described on clinicaltrials.gov. Ex. 1013 (NCT657) at 15. According to the version of NCT657 captured by the Wayback Machine on June 25, 2011, the details of NCT657 were “Last Updated on March 16, 2011.” *Id.* Novo Nordisk was the sponsor of NCT657. *Id.* Christine B. Jensen, M.D., Ph.D., of Novo Nordisk is listed as the study director for NCT657. *Id.* at 17. Christine Bjoern Jensen is also a named inventor of the ’462 patent. Ex. 1001 (’462 patent) at 1.

122. The official title of NCT657 is “Investigation of Safety and Efficacy of Five Doses of Semaglutide Versus Placebo and Open-label Liraglutide, as Add on Therapy, in Subjects Diagnosed With Type 2 Diabetes Currently Treated With Metformin or Controlled With Diet and Exercise A 12 Week Multi-centre, Multi National, Double-blind, Placebo-controlled, Randomised, Nine Armed Parallel Group, Dose Finding Trial.” Ex. 1013 (NCT657) at 15. The Purpose section of NCT657 states:

> This trial was conducted in Europe, Asia and Africa. Study participants were randomised evenly to treatment with semaglutide (0.1 mg QW - 1.6 mg QW, 6 treatment arms, placebo or liraglutide (1.2 mg QD, or 1.8 mg QD). Treatment allocation to semaglutide or placebo was double-blind, whereas liraglutide treatment was administered open-label. Primary efficacy parameter was HbA1c and the treatment duration was 12 weeks.

Id. at 15.

123. NCT657 listed an enrollment of 415 patients. *Id.* at 15. The primary outcome measures listed for NCT657 was HbA_{1c} level after 12 weeks treatment. *Id.* at 15. Secondary outcome measures in NCT657 included, among others, the percentage of subjects with adverse events or with hypoglycaemic episode. *Id.* at 15.

124. NCT657 had six experimental arms in the clinical trial (A-F), which included subcutaneous injections of semaglutide, once weekly, 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. Skilled artisans would have understood that "with titration" meant that the recited dose amount was reached by starting from a lower dose amount and then increasing the dose until reaching the final level.

125. NCT657 also included six placebo comparator arms (G1-G6) and two Experimental arms (H and I), which included subcutaneous injections once daily of 1.2 and 1.8 mg of liraglutide, respectively. *Id.* at 16.

2. NCT773 [Ex. 1014]

126. Clinical Trial No. NCT00851773 ("NCT773") is titled "Safety, Tolerability, and Profile of Action of Drug in the Body of NN9535 in Healthy Male Japanese and Caucasian Subject" and was listed and described on clinicaltrials.gov. *See* Ex. 1014 (NCT773) at 7. According to the version of NCT773 captured by the Wayback Machine on October 22, 2011, the details of NCT773 were "Last Updated on July 15, 2010." *Id.* Novo Nordisk was the sponsor of NCT773. *Id.* Jean Lynge, MSc, PhD, of Novo Nordisk is listed as the study director for NCT773. *Id.* at 8. NCT773 disclosed that the start date of the study was February 2009 and that the competition date was August 2009. *Id.* at 7.

127. The Purpose of NCT773 disclosed:

> 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.

128. NCT773 listed an enrollment of 84 patients. *Id.* at 7. The primary outcome measures listed for NCT773 was adverse events at all scheduled visits following screening. *Id*. Secondary outcome measures in NCT773 included, among others, the frequency of hypoglycaemic episodes and vital signs. *Id*.

129. NCT773 included five experimental arms (A-E), which included once weekly subcutaneous injections of semaglutide (NN9535) for eight weeks at the following doses:

(A) 0.1 mg once weekly,

(B) 0.2 mg once weekly,

(C) 0.4 mg once weekly,

(D) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks,

(E) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.2 mg once weekly for 6 weeks.

Id. at 7. NCT773 also included five placebo comparator arms (F1-F5). *Id.* at 7-8.

130. An earlier version of NCT773 captured by the Wayback Machine on September 11, 2009 that states it was "Last Updated on August 26, 2009" ("2009 NCT773") disclosed that the earlier NCT773 protocol included seven Experimental arms (A-G), which included once weekly subcutaneous injections of semaglutide (NN9535) for eight weeks at the following doses:

(A) 0.1 mg once weekly,

(B) 0.2 mg once weekly,

(C) 0.4 mg once weekly,

(D) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 7 weeks,

(E) 0.8 mg once weekly,

(F) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, 1.6 mg once weekly for 6 weeks, and

(G) 0.4 mg once weekly for 1 week, 0.8 mg once weekly for 1 week, followed by once weekly injections for 6 weeks. Dose to be determined based on safety and tolerability of previous dose steps. This dose is optional and will be implemented if the 0.8 mg is tolerated but the 1.6 mg is not.

Id. at 11. Thus, in the earlier protocol from 2009 NCT773, there were seven experimental arms and the highest dose tested was 1.6 mg semaglutide, compared with the later updated NCT773 protocol that only included five experimental arms with the highest dose tested being 1.2 mg semaglutide. *Compare id.* at 11 *with id.* at 7.

3. Public Availability of ClinicalTrials.gov

131. I understand that a prior art reference is proven to be a "printed publication" upon a satisfactory showing that such document has been disseminated or otherwise made available to the extent that persons interested and ordinarily skilled in the subject matter or art, exercising reasonable diligence, can locate it. I

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. I also understand that documents obtained via the Wayback Machine[5] are presumed to be publicly accessible at the date and time provided in the time stamp.

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[5] As described in the U.S. Patent Office's Manual of Patenting Examining Procedure (MPEP), I understand the Wayback Machine is a digital library maintained by the Internet Archive for viewing information on archived digital Internet webpages. *See* MPEP § 2128.II.E ("Printed Publications" as Prior Art) ("The Wayback Machine® is a digital library maintained by the Internet Archive (a non-profit organization) for viewing information on archived digital Internet webpages. Simply, the Wayback Machine® uses software programs, known as crawlers, to surf the Internet and automatically store copies of Web objects (Web pages, images, videos, etc.), preserving these objects as they exist at the point and time of capture. These Web objects are stored as Web captures with the capture time/date in the form of a time stamp and the URL of the original website of capture. Accordingly, the Wayback Machine® provides the ability to view and browse Internet information that may no longer be available on the original website. … Prior art obtained via the Wayback Machine® sets forth a prima facie case that the art was publicly accessible at the

132. Exhibits 1013 and 1014 are archived versions of pages from the ClinicalTrials.gov website, as stored on the Wayback Machine website. These Exhibits would have been available on the ClinicalTrials.gov website before the priority date and would have been easily located by a POSA using the robust search tools then available on the ClinicalTrials.gov website.

133. ClinicalTrials.gov is a website that "provides patients, their family members, health care professionals, researchers, and the public with easy access to information on publicly and privately supported clinical studies on a wide range of diseases and conditions." Ex. 1076 (ClinicalTrials.gov Background) at 1. ClinicalTrials.gov is maintained by the National Library of Medicine ("NLM") at the National Institutes of Health ("NIH"). *Id.* In my opinion, the NIH is one of the most reliable sources of information in the medical field. POSAs would understand that information provided by the NIH, including through the ClinicalTrials.gov website, was reliable, trustworthy, and accurate.

134. It is my understanding that "ClinicalTrials.gov was created as a result of the Food and Drug Administration Modernization Act of 1997 ("FDAMA")." *See*

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date and time provided in the time stamp."). Available at: https://www.uspto.gov/web/offices/pac/mpep/s2128.html (last accessed March 11, 2023).

Ex. 1076 (ClinicalTrials.gov Background) at 2; *see also* 42 U.S.C. § 282(i) ("Data bank of information on clinical trials for drugs for serious or life-threatening diseases and conditions"). I understand that "FDAMA required the U.S. Department of Health and Human Services (HHS), through NIH, to establish a registry of clinical trials information for both federally and privately funded trials conducted under investigational new drug applications to test the effectiveness of experimental drugs for serious or life-threatening diseases or conditions." *Id.* I understand that "NIH and the Food and Drug Administration (FDA) worked together to develop the site, which was made available to the public in February 2000." *Id.*

135. In 2004, ClinicalTrials.gov was awarded the *Innovation in American Government Award* from Harvard's Kennedy School ("Harvard"). Ex. 1077 (Harvard Award) at 1. Harvard noted that before ClinicalTrials.gov came online, "those wishing to find information on diseases and treatment options often find themselves sifting through too many websites with too much information and too little plain language." *Id.* Harvard stated:

> [u]ntil 2000, this problem was particularly pressing for those who wished to find information on clinical trials of medical treatments. 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.'

Id. at 1-2. Harvard further noted that "ClinicalTrials.gov was designed to be a centralized, standardized, and current resource for those seeking information on clinical studies." *Id.* at 2. Harvard explained that

> [t]he 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.

Id. Harvard went on to state:

> ClinicalTrials.gov has developed a successful model for the creation and maintenance of a system that processes and presents large amounts of specialized information to a wide range of users. The site now contains records from trials in all 50 states and more than 90 countries 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.

Id.

136. The importance of ClinicalTrials.gov as a research tool was widely recognized in the prior art. *See* Ex. 1062 (Zarin) at 2 ("The ClinicalTrials.gov trial registry was launched more than a decade ago. Since that time, it has been evolving in response to various policy initiatives. 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."); Ex. 1063 (Kirillova).

137. Searching ClinicalTrials.gov did not require registration, subscription fees, or personal identification. Ex. 1076 (ClinicalTrials.gov Background) at 2. The ability of POSAs to search, navigate and locate information of interest was unambiguously demonstrated in the prior art medical literature. For example, in Monami, a 2012 article in Experimental Diabetes Research, researchers conducted a meta-analysis of clinical trials on humans reported through December 15, 2011, using GLP-1 receptor agonists, including exenatide, liraglutide, albiglutide, semaglutide, and lixisenatide. Ex. 1064 (Monami) at 2. Data sources for the trial

included, inter alia, "a search of http://www.clinicaltrials.gov/ website." Further, "[r]esults of those trials were retrieved, if available, on http://www.novonordisk-trials.com/ or http://www.clinicaltrials.org/." *Id.* (emphasis added). Thus, Monami made clear that, at the priority date, researchers were able to access ClinicalTrials.gov and to locate and obtain information on clinical trials. *See also* Ex. 1065 (Tasneem) at 3 ("A dataset comprising 96,346 clinical studies was downloaded from ClinicalTrials.gov in XML format on September 27, 2010. We chose ClinicalTrials.gov for our 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.").

138. Thus, as of the priority date, POSAs knew that ClinicalTrials.gov contained valuable and readily accessible information on clinical trials. A POSA interested in clinical trials involving GLP-1 receptor agonists would have easily found Exhibits 1013 and 1014 on the ClinicalTrials.gov website. Indeed, in my own experience before and around the priority date, I routinely accessed the ClinicalTrials.gov website, utilized its search tools, and reviewed and analyzed the data on the site. In my experience, as reflected in the prior art, the ClinicalTrials.gov website was readily accessible and easily navigable to POSAs as of the priority date.

E. KNUDSEN 2004 [EX. 1032]

139. "Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes" ("Knudsen 2004") is the title of a journal article authored by Lotte Bjerre Knudsen at Novo Nordisk, published in 2004, before the earliest claimed priority date of the '462 patent. Ex. 1032 (Knudsen 2004) at 1.

140. Knudsen 2004 disclosed the amino acid sequences of GLP-1 and exendin-4. *Id.* at 3, Fig. 1. Knudsen also disclosed the structures of liraglutide and exenatide. *Id.* at 3, Fig. 2. Figure 3 of Knudsen 2004 disclosed the structure-activity relationship (SAR) of GLP-1 including the sites essential for binding to the GLP-1 receptor. *Id.* at 3, Fig. 3.

141. 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," and stated "that long-term efficacy can be obtained without major gastrointestinal side effects." *Id.* at 1-2. Knudsen disclosed, "[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.* at 4.

F. LUND [EX. 1035]

142. "Emerging GLP-1 Receptor Agonists" ("Lund") is the title of a review article authored by Asger Lund, Filip K. Knop, and Tina Vilsbøll, which was

published online on September 9, 2011,[6] before the earliest claimed priority date of the ’462 patent. Ex. 1035 (Lund) at 1.

143. Lund provided “an overview of the clinical data on the currently available GLP-1R agonists used for treatment of type 2 diabetes, exenatide and liraglutide, as well as the emerging GLP-1R agonists including the long-acting compounds.” *Id.* at Abstract. Lund disclosed, “[t]he long-acting GLP-1R agonists in late development may improve the effects of GLP-1 even further with optimized pharmacokinetic profiles resulting in fewer side effects. Meta-analyses have shown promising effects on cardiovascular disease.” *Id.* at 1.

144. Figure 1 of Lund (reproduced below) disclosed a list of GLP-1 receptor agonists, “GLP-1-based” and “Exendin-4-based,” for subcutaneous injection:

[6] My opinion that the claims of the ’462 patent are anticipated and obvious does not require the disclosures of Lund (Ex. 1035). Exhibit 1035 merely confirms the other prior art set forth in this declaration.

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

Id. at 3, Fig. 1.

145. Table 1 of Lund (reproduced below) disclosed an overview of the existing and emerging GLP-1R agonists and their state of development and ongoing trials:

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

CVD: Cardiovascular disease; GLP-1R: Glucagon-like peptide-1 receptor.

Id. at 4, Table 1.

146. Table 2 of Lund (reproduced below) disclosed the amino acid structures of GLP-1 and the GLP-1R agonists on the market or in late clinical development:

Name	Structure
Native GLP-1	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg
Liraglutide	His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Arg-Gly-Arg-Gly | Glu-C16 fatty acid
Albiglutide	(His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg)$_2$ – linked to human albumin
Exenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser
Lixisenatide	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser-Lys-Lys-Lys-Lys-Lys-Lys
CJC-1134-PC	His-Gly-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Leu-Ser-Lys-Gln-Met-Glu-Glu-Glu-Ala-Val-Arg-Leu-Phe-Ile-Glu-Trp-Leu-Lys-Asn-Gly-Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser-Lys-C13H19O6N3 (linker molecule)

GLP-1: Glucagon-like peptide-1; GLP-1R: Glucagon-like peptide-1 receptor.

Id. at 4, Table 2.

147. Lund also disclosed a summary of the GLP-1 receptor agonists including exenatide once weekly, lixisenatide, CJC-1134-PC, albiglutide, dulaglutide, and semaglutide. *Id.* at 5-8.

148. 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." *Id.* at 7. Lund also disclosed:

> So far, three Phase I studies looking at pharmacokinetics and safety of semaglutide (NCT00813020, NCT00833716 and NCT00851773), and one Phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide have been completed (NCT00696657). At the end of March 2011, a Phase I study looking at the influence of the pharmacokinetics of

> an oral contraceptive combination drug after administration of semaglutide was initiated (NCT01324505).

Id. at 7-8.

G. SEINO [EX. 1038]

149. "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" ("Seino") is the title of a journal article authored by Y. Seino, M.F. Rasmussen, M. Zdravkovic, K. Kaku. Ex. 1038 (Seino) at 1. Seino was published May 20, 2008, before the earliest claimed priority date of the '462 patent. *Id.*

150. Seino disclosed "[i]n this study, we investigated efficacy and safety from a dose response perspective with four doses of liraglutide and placebo in Japanese patients with type 2 diabetes." *Id.* at 6. The study was "a multicenter, double blind, randomized, parallel group phase 2 trial to evaluate the dose response relationship on glycemic control of four doses of liraglutide and placebo in Japanese subjects with type 2 diabetes." *Id.* at 2. Seino disclosed "[t]he primary efficacy endpoint was HbA_{1c} after 14 weeks of treatment, with other measures of glycemic control (fasting plasma glucose (FPG), postprandial plasma glucose (PPG), self monitored plasma glucose profile) as secondary endpoints." *Id.* "Patients were

randomized at the end of the run in period to liraglutide or placebo in four cohorts, each planned to contain 50 patients; in each cohort a planned 40 patients received one of four liraglutide doses (0.1 mg/day; 0.3 mg/day; 0.6 mg/day or 0.9 mg/day) and 10 received placebo. Liraglutide doses in the 0.6 and 0.9 mg/day cohorts were increased from a starting dose of 0.3 0.6 mg/day after 1 week and, in the 0.9 mg/day cohort, by a further 0.3 mg/day after 2 weeks." *Id.*

151. Regarding the results of the study, Seino stated: "[w]e demonstrated significantly dose dependent improvements in key parameters of glycemia HbA_{1c}, FPG, PPG, seven point self monitored plasma glucose and beta cell function following 14 weeks' treatment with liraglutide." *Id.* Seino reported "[a] clear dose response relationship for HbA_{1c} was shown in this study." *Id.* "All doses of liraglutide tested showed a degree of efficacy, with a plateau of dose response at 0.9 mg/day. A dose of 0.9 mg/day appears to be highly effective and, of the doses tested, offers the optimal efficacy/tolerability balance in Japanese patients with type 2 diabetes." *Id.* Seino disclosed that "there was no treatment related development of liraglutide antibodies during the trial." *Id.* Figure 1 of Seino shows the dose-response for HbA_{1c} with increasing doses of liraglutide. *Id.* at 4. The data in Figure 1 are the means ± standard error (S.E.) for HbA_{1c} after 14 weeks. *Id.*

H. VICTOZA LABEL [EX. 1039]

152. The Victoza® label, issued January 2010, provides the prescribing information of Victoza®, approved by FDA in 2010 ("Victoza label"). *See* Ex. 1039 (Victoza label) at 9.

153. The Victoza label disclosed, "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." *Id.* at 2. "Victoza contains liraglutide, an analog of human GLP-1" that "acts as a GLP-1 receptor agonist." *Id.* at 5.

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

155. The Victoza label disclosed:

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

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

Id. at 5-6.

156. The Victoza label disclosed:

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

Id. at 6.

157. The Victoza label also disclosed the following regimen:

- Administer once daily at any time of day, independently of meals (2).

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

Id. at 2.

158. The Victoza label disclosed that Victoza was available as a "[s]olution for subcutaneous injection," in a "pre-filled, multi-dose pen that delivers doses of 0.6 mg, 1.2 mg, or 1.8 mg." *Id.* at 2.

I. SHARGEL [EX. 1045]

159. "Applied Biopharmaceutics and Pharmacokinetics" ("Shargel") is the title of a book edited by Leon Shargel, Ph.D., RPh, Susanna Wu-Pong, Ph.D., RPh,

and Andrew B.C. Yu, Ph.D., RPh, which was published in 2005, before the earliest claimed priority date of the ’462 patent. Ex. 1045 (Shargel) at 1-2.

160. Shargel disclosed that “[p]harmacokinetics is the science of the kinetics of drug absorption, distribution, and elimination (ie, excretion and metabolism).” *Id.* at 15. Shargel disclosed “[c]haracterization of drug disposition is an important prerequisite for determination or modification of dosing regimens for patients.” *Id*. “The study of pharmacokinetics involves both experimental and theoretical approaches.” *Id.* Shargel disclosed “[p]harmacodynamics refers to the relationship between the drug concentation at the site of action (receptor) and pharamacologi response, including biuochemical and physiologic effects that influence the interaction of drug with the receptor.” *Id.* at 16.

161. Shargel provided a schematic of a plasma drug concentration-time curve showing parameters such as C_{max} (maximum concentration), t_{max} (time of maximum), and AUC (Area Under the Curve). *Id.* at 40, Figure 15-1. Shargel disclosed “[t]he onset, intensity, and duration of the pharmacologic effect depend on the dose and the pharmacokinetics of the drug.” *See id.* at 81. Shargel continued, “[a]s the dose of the drug increases, the concentration at the receptor site increases, and the pharmacologic response (effect) increases up to a maximum effect. A plot of the pharmacologic effect to dose on a linear scale generally results in a hyperbolic

curve with maximum pharmacologic effect (E_{max}) at the plateau on the dose-response curve." *Id.* at 81-82, Fig. 19-1.

J. TAMIMI [EX. 1047]

162. "Drug Development: From Concept to Marketing!" is the title of a minireview authored by Nihad A.M. Tamimi and Peter Ellis, which was published in 2009, before the earliest claimed priority date of the '462 patent. Ex. 1047 (Tamimi) at 1.

163. Tamimi provided a summary of the development of a drug, including discovery, pre-clinical studies, phase I-III studies, approval, and post approval. *See id.* at 1-6, Fig. 1. Tamini disclosed that "[d]rug development is a long, expensive and highly regulated process." *Id.* at 6. Tamimi disclosed that after compounds have been screened and positively selected, "functional biochemical and pharmacological testing in vitro, followed by pharmacodynamic and pharmacokinetic testing in vitro and in vivo" is performed. *Id.* at 3. Tamimi disclosed a suitable formulation is then developed for the drug and the drug is "progressed through the required toxicology testing (including genotoxicity, safety pharmacology in all biological systems, single and multiple dose toxicity and toxicokinetic studies) to enable the first in human and subsequent clinical studies." *Id.*

164. Tamimi also disclosed, "[c]linical phases of drug development include phase I in healthy volunteers to assess primarily pharmacokinetics, safety and toleration, phase II in a cohort of patients with the target disease to establish efficacy and dose-response relationship and large-scale phase Ill studies to confirm safety and efficacy." *Id.* at 1. Tamimi disclosed "[p]hase I studies require approval from an ethics committee and the relevant regulatory agency." *Id.* at 3. "Phase I studies usually start with single sub-pharmacological doses which are escalated gradually and followed by multiple doses." *Id.* Tamimi disclosed "[s]topping rules to dose escalation include severe adverse events, clinically significant ECG abnormalities and clinically significant laboratory abnormalities." *Id.* "Phase I studies require approval from an ethics committee and the relevant regulatory agency." *Id.* "Other phase I studies to support drug development are conducted throughout phase II and II of development." *Id.* Regarding phase II studies, Tamimi disclosed "[o]nce the drug's safety, pharmacokinetics and dose selection has been established in healthy volunteers, the next step is to investigate the efficacy and safety of the drug in the target population." *Id.* Tamimi disclosed that phase II studies are usually divided into phase IIa and phase Ilb but occasionally they are combined. *Id.* "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." *Id.* Tamimi disclosed that phase III studies are "the final stage of drug development prior to registration and will confirm the clinical doses, frequency of timing of administration for approval." *Id.*

K. FDA Exposure Response 2003 [Ex. 1048]

165. "Guidance for Industry, *Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications*" was provided by the U.S. Department of Health and Human Services of the FDA in April 2003, before the earliest claimed priority date of the '462 patent. Ex. 1048 (FDA Exposure Response 2003) at 1.

166. FDA Exposure Response 2003 stated that "[e]xposure-response information is at the heart of any determination of the safety and effectiveness of drugs. That is, a drug can be determined to be safe and effective only when the relationship of beneficial and adverse effects to a defined exposure is known." FDA Exposure Response 2003 further stated "[t]he dose-response study is a particularly informative design, allowing observations of benefits and risks at different doses and therefore providing an ability to weigh the benefits and risks when choosing doses. The dose-response study can help ensure that excessive doses (beyond those that add to efficacy) are not used, offering some protection against unexpected and unrecognized dose-related toxicity." *Id.* at 7. FDA Exposure Response 2003 stated:

> For the purposes of this guidance, we are using the broad term *exposure* to refer to dose (drug input to the body) and various measures of acute or integrated drug concentrations in plasma and other biological fluid (e.g., Cmax, Cmin, Css, AUC). Similarly, *response* refers to a direct measure of the pharmacologic effect of the drug. Response includes a broad range of endpoints or biomarkers ranging from the clinically remote biomarkers (e.g., receptor occupancy) to a presumed mechanistic effect (e.g., ACE inhibition), to a potential or accepted *surrogate* (e.g., effects on blood pressure, lipids, or cardiac output), and to the full range of short-term or longterm clinical effects related to either efficacy or safety.

Id. at 5.

L. ICH 1994 [Ex. 1049]

167. "International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability" ("ICH 1994") is the title of a notice published in the Federal Register on November 9, 1994, before the earliest claimed priority date of the '462 patent. Ex. 1049 (ICH 1994) at 1.

168. ICH 1994 disclosed that "[t]he Food and Drug Administration (FDA) is publishing a final guideline entitled 'Dose-Response Information To Support Drug Registration.'" *Id.* ICH 1994 stated "[t]his guideline was prepared by the Efficacy Expert Working Group of the International Conference on Harmonisation of

Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH)."

ICH 1994 explained:

> The guideline describes why dose-response information is useful and how it should be obtained in the course of drug development. This information can help identify an appropriate starting dose as well as how to adjust dosage to the needs of a particular patient. It can also identify the maximum dosage beyond which any added benefits to the patient would be unlikely or would produce unacceptable side effects. This guideline is intended to help ensure that dose response information to support drug registration is generated according to sound scientific principles.

Id. at 1.

169. ICH 1994 disclosed that "ICH is concerned with harmonization of technical requirements for the registration of pharmaceutical products among three regions: The European Union, Japan, and the United States." *Id.*

170. ICH 1994 provided the text of the final guideline titled "Dose-Response Information to Support Drug Registration." *Id.* Under a heading titled "Purpose of Dose-Response Information," the final guideline stated:

> Knowledge of the relationships among dose, drug concentration in blood, and clinical response (effectiveness and undesirable effects) is important for the safe and effective use of drugs in individual patients. This information can help identify an appropriate starting dose, the best way to adjust dosage to the needs of a particular patient, and a dose

> beyond which increases would unlikely to provide added benefit or would produce unacceptable side effects.

Id. at 1.

171. The final guideline continued:

> Historically, drugs have often been initially marketed at what were later recognized as excessive doses (i.e., doses well onto the plateau of the dose-response curve for the desired effect), sometimes with adverse consequences (e.g., hypokalemia and other metabolic disturbances with thiazide-type diuretics in hypertension). This situation has been improved by attempts to find the smallest dose with a discernible useful effect or a maximum dose beyond which no further beneficial effect is seen, but practical study designs do not exist to allow for precise determination of these doses.

Id. at 2.

172. Under a heading titled "Use of Dose-Response Information in Choosing Doses," the final guideline disclosed:

> What is most helpful in choosing the starting dose of a drug is knowing the shape and location of the population (group) average dose-response curve for both desirable and undesirable effects. Selection of dose is best based on that information, together with a judgment about the relative importance of desirable and undesirable effects.

Id. at 2.

173. Under a heading titled "Study Designs for Assessing Dose Response," the final guideline stated "[i]t is important to choose as wide a range of doses as is compatible with practicality and patient safety to discern clinically meaningful differences." *Id.* at 4.

174. Under a heading titled "Guidance and Advice," the final guideline stated "[d]epending on circumstances (the disease, the drug's toxicity), the starting dose may range from a low dose with some useful effect to a dose that is at or near the full-effect dose." *Id.* at 6.

M. KNUDSEN 2010B [EX. 1066]

175. "Liraglutide: The Therapeutic Promise from Animal Models" ("Knudsen 2010b") is the title of a review paper authored by Lotte Bjerre Knudsen at Novo Nordisk A/S, published in October 2010, before the earliest claimed priority date of the '462 patent. Ex. 1066 (Knudsen 2010b) at 1.

176. Knudsen 2010b disclosed "[p]reclinical work is a necessary precursor to human studies: assessment of toxicity in a preclinical setting is a legal requirement, but preclinical studies also gather important preliminary data on pharmacokinetics and pharmacodynamics." *Id.* Knudsen 2010b also disclosed "[a] large body of data in any preclinical programme is generated from *in vitro* investigations; however, normal animals and animal models of the disease state

allow us to examine the effects of a new drug on the complex interplay of metabolic processes." *Id.*

N. ADDITIONAL PRIOR ART AND REFERENCES

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

IX. UNPATENTABILITY OF THE '462 PATENT

A. GROUND 1: WO421 ANTICIPATED CLAIMS 1-3 OF THE '462 PATENT

178. As described below, in my opinion, claims 1-3 of the '462 patent are unpatentable as anticipated by WO421.

1. Teachings of WO421

179. The teachings of WO421 are detailed above in paragraphs 106-111.

2. WO421 anticipated claim 1

180. Independent claim 1 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, WO421 taught each element of claim 1 of the '462 patent.

181. *First*, WO421 disclosed the preamble of claim 1 of the '462 patent. As I discussed previously, in my opinion, "[a]method for treating type 2 diabetes," should be interpreted broadly. *See supra* ¶¶ 56-60.

182. The specification of WO421 stated that "[t]he present invention relates to methods for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus." Ex. 1011 (WO421) at 2:4-5.

183. Further, claim 17 of WO421 recites:

> A GLP-1 receptor agonist selected from exenatide, exenatide LAR, liraglutide, taspoglutide, ***semaglutide***, albiglutide, lixisenatide and dulaglutide, ***for use in a method of treating type 2 diabetes***, obesity or both, said method comprising administration (e.g. separate, sequential or simultaneous administration) of the GLP-1 receptor agonist and a DPP-4 inhibitor which is preferably linagliptin.

Id. at 65:27-31 (emphasis added). Thus, the specification and claim 17 of WO421 taught the preamble, "[a]method for treating type 2 diabetes."

184. *Second*, WO421 also disclosed the element "comprising administration of semaglutide" of claim 1. It is my understanding from counsel that the term "comprising" means that the claim limitations that follow the term "comprising" must be present in an embodiment of the claims, but that the term is "open," meaning

that additional limitations may also be present in an embodiment of the claims. Therefore, while claim 1 of the '462 patent must include "administering semaglutide once weekly in an amount of 1.0 mg to a subject in need thereof," claim 1 also allows for administration of semaglutide in combination with another drug, including before, after, or with other drugs.

185. The specification of WO421 disclosed "a method for treating and/or preventing metabolic diseases, especially type 2 diabetes mellitus . . . comprising the combined (e.g., simultaneous, ***separate*** or sequential) administration of an effective amount of a GLP-1 receptor agonist … and … an effective amount of a DDP-4 inhibitor." Ex. 1011 (WO421) at 11:14-20 (emphasis added). WO421 taught that "[p]referred examples of GLP-1 receptor agonists … are …. semaglutide." *Id.* 34:20-22.

186. In addition, claim 17 of WO421 recited "semaglutide … for use in a method of treating type 2 diabetes … said method comprising administration (e.g., ***separate***, sequential or simultaneous administration) of the [semaglutide] and a DPP-4 inhibitor." *Id.* at 65:26-31 (emphasis added). Further, WO421 disclosed that administration of the combination therapy of a GLP-1 receptor agonist and DPP-4 "may refer to first line, second line or third line therapy, or initial or add-on combination therapy or replacement therapy." *Id.* at 37:22-24. WO421 also disclosed that administration of the combination therapy may occur by administering

the active components as separate formulations "simultaneously, ***separately***, sequentially, or chronologically staggered." *Id.* at 37:2-24 (emphasis added).

187. In my opinion, skilled artisans would understand these disclosures to include administration of semaglutide alone, including as a separate course of treatment. Thus, both the specification and claim 17 of WO421 disclosed the element "comprising administration of semaglutide."

188. Moreover, because the scope of "[a]method for treating type 2 diabetes, *comprising* administering semaglutide" in claim 1 of the '462 patent may include administering semaglutide before, after, or with other drugs, the specification and claim 17 of WO421 disclosed the element "comprising administration of semaglutide" of claim 1.

189. *Third*, WO421 also disclosed the element "once weekly in an amount of 1.0 mg." In particular, the specification of WO421 disclosed that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1 to 1.6 mg)." *Id.* at 44:14. In my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg increments, including 0.6 mg, 1.2 mg, and 1.8 mg. *See* Ex. 1039 (Victoza label) at 2. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg,

0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk's phase II clinical study (*see* Ex. 1013 (NCT657) at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk's phase I clinical study (*see* Ex. 1014 (NCT773) at 7). Therefore, a POSA would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisioned all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg).

190. Moreover, skilled artisans would have been aware of Novo Nordisk's phase I and phase II clinical trials testing once weekly doses ranging from 0.1-1.6 mg semaglutide. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. Similar to the liraglutide phase II study about which Seino reported that "[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy" (Ex. 1038 (Seino) at 6), skilled artisans would similarly expect that all of the once weekly doses of semaglutide tested in NCT657 and NCT773 would exhibit some degree of efficacy.

191. Thus, WO421 disclosed the element "once weekly in an amount of 1.0 mg" of claim 1.

192. Moreover, because claim 17 of WO421 recited "[a] GLP-1 receptor agonist selected from . . . semaglutide . . . for use in a method of treating type 2 diabetes . . . said method comprising administration . . . of the GLP-1 receptor agonist," a POSA would immediately envision using the once weekly dose of "0.1 to 1.6 mg" semaglutide disclosed in WO421 for administration for at least the same reasons as described above. Thus, claim 17 of WO421 also disclosed the element "once weekly in an amount of 1.0 mg" of claim 1.

193. *Fourth*, WO421 disclosed the element "to a subject in need thereof." Throughout the disclosure, WO421 taught that the therapy should be for the treatment of diabetes in a human patient. *See., e.g.,* Ex. 1011 (WO421) at 37:3-5. The WO421 also disclosed that therapies "may be used in [drug] naïve patients," or "patients with advanced or late-stage type 2 diabetes" or "patients ineligible for metformin" or "patients having…renal disease [or] … disfunction." *Id.* at 9:35-11:7. Thus, WO421 disclosed the element "to a subject in need thereof" of claim 1.

194. Claim 17 of WO421 also disclosed "to a subject in need thereof" because a skilled artisan would have the understanding that "administration of the GLP-1 receptor agonist" (semaglutide) "for use in a method of treating type 2 diabetes" would necessarily be for the purposes of administering to a human patient to treat type 2 diabetes.

195. Thus, for the aforementioned reasons, both the specification and claim 17 of WO421 anticipated claim 1 of the ’462 patent.

3. WO421 anticipated claim 2

196. In my opinion, WO421 anticipated claim 2 of the ’462 patent. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.”

197. WO421 disclosed “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” Ex. 1011 (WO421) at 44:13. In my opinion, skilled artisans would have known that subcutaneous injection is a type of parenteral administration. *See, e.g.,* Ex. 1015 (WO537) at 35:15-16 (“Parenteral administration may be performed by subcutaneous . . . injection.”).

198. The specification of WO421 and claim 17 of WO421 therefore anticipated claim 2 of the ’462 patent.

4. WO421 anticipated claim 3

199. In my opinion, WO421 anticipated claim 3 of the ’462 patent. Claim 3 depends from claim 2 and recites, “[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection.”

200. WO421 disclosed “[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg).” Ex. 1011 (WO421) at 44:13. In my opinion,

skilled artisans would have known that a subcutaneous injection is necessarily a solution.

201. The specification of WO421 and claim 17 of WO421 therefore anticipated claim 3 of the ’462 patent.

B. GROUND 2: LOVSHIN ANTICIPATED CLAIMS 1-3 OF THE ’462 PATENT

202. As described below, in my opinion, claims 1-3 of the ’462 patent are unpatentable as anticipated by Lovshin.

1. Teachings of Lovshin

203. The teachings of Lovshin are detailed above in paragraphs 112-115.

2. Lovshin anticipated claim 1

204. Independent claim 1 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 element of claim 1 of the ’462 patent.

205. *First*, Lovshin disclosed the preamble of claim 1 of the ’462 patent. As I discussed previously, in my opinion, “[a]method for treating type 2 diabetes,” should be interpreted broadly. *See supra* ¶¶ 56-60.

206. Lovshin disclosed “[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.” Ex. 1012 (Lovshin) at 12. Lovshin also

disclosed, "multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1)." *Id.* at 5.

207. Thus, Lovshin taught the preamble, "[a]method for treating type 2 diabetes."

208. *Second*, Lovshin also disclosed the element "comprising administration of semaglutide" of claim 1. Lovshin disclosed, "multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1)." *Id.* at 5. A POSA would have known that NN9535 was semaglutide.[7] Moreover, if semaglutide was being investigated in phase I-II studies, a POSA would have known that this involved administering semaglutide to subjects in the phase I-II studies. Thus, Lovshin disclosed the element "comprising administration of semaglutide" of claim 1.

209. *Third*, Lovshin also disclosed the element "once weekly in an amount of 1.0 mg." In particular, Table 1 of Lovshin disclosed that NN9535 (semaglutide) was being investigated at a dose of "0.1-1.6 mg once weekly." *Id.* at 2, Table 1. In

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[7] *See* Ex. 1060 (WO193) at 35:18 ("semaglutide/NN9535 (Novo Nordisk)"); *see also* Ex. 1035 (Lund) at 4, Table 1 ("Semaglutide (NN9535) Novo Nordisk").

my opinion, a skilled artisan would have understood that the disclosed range included a discrete number of dosing steps, proceeding in increments of no less than 0.1 mg. For example, skilled artisans would have known that the related GLP-1 receptor agonist, liraglutide, was administered in doses of 0.6 mg, 1.2 mg, and 1.8 mg. *See* Ex. 1039 (Victoza label) at 2. Further, skilled artisans would have known that weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg were being tested in Novo Nordisk's phase II clinical study (*see* Ex. 1013 (NCT657) at 15-16) and weekly semaglutide doses of 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.2 mg were being tested in Novo Nordisk's phase I clinical study (*see* Ex. 1014 (NCT773) at 7). Therefore, a POSA would have pursued dosing increments of no less than 0.1 mg/dose and would have immediately envisioned all the options in that range at the smallest reasonable step size, which would include at most a group of just 16 doses (i.e., 0.1 mg, 0.2 mg, 0.3 mg, 0.4 mg, 0.5 mg, 0.6 mg, 0.7 mg, 0.8 mg, 0.9 mg, 1.0 mg, 1.1 mg, 1.2 mg, 1.3 mg, 1.4 mg, 1.5 mg, and 1.6 mg).

210. Moreover, skilled artisans would have been aware of Novo Nordisk's phase I and phase II clinical trials testing once weekly doses ranging from 0.1-1.6 mg semaglutide. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. Similar to the liraglutide phase II study disclosed in Seino in which "[a]ll doses [liraglutide 0.1 mg/day, 0.3 mg/day, 0.6 mg/day, and 0.9 mg/day] tested showed a degree of efficacy" (Ex. 1038 (Seino) at 6), skilled artisans would similarly expect that all once

weekly doses of semaglutide tested in NCT657 and NCT773 would exhibit some degree of efficacy.

211. Thus, Lovshin disclosed the element "once weekly in an amount of 1.0 mg" of claim 1.

212. *Fourth*, Lovshin disclosed the element "to a subject in need thereof." Lovshin disclosed, "multiple once-weekly GLP-1 therapies are under active clinical investigation in phase I-II studies (NN9535, LY2199265, and a pegylated GLP-1 molecule, LY2428757; see Table 1)." Ex. 1012 (Lovshin) at 5. If semaglutide was being investigated in phase I-II studies, a POSA would have known that this involved administering semaglutide to subjects in the phase I-II studies. Thus, Lovshin disclosed the element "to a subject in need thereof" of claim 1.

213. Thus, for the aforementioned reasons, Lovshin anticipated claim 1 of the '462 patent.

3. Lovshin anticipated claim 2

214. In my opinion, Lovshin anticipated claim 2 of the '462 patent. Claim 2 depends from claim 1 and recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration."

215. Lovshin disclosed that the dose of NN9535 (semaglutide) to be administered to a patient is "0.1–1.6 mg once weekly," given by "subcutaneous injection" to treat type 2 diabetes. Ex. 1012 (Lovshin) at 2. In my opinion, skilled

artisans would have known that a subcutaneous injection is a type of parenteral administration. *See, e.g.,* Ex. 1015 (WO537) at 35:15-16 ("Parenteral administration may be performed by subcutaneous . . . injection.").

216. Lovshin therefore anticipated claim 2 of the '462 patent.

4. Lovshin anticipated claim 3

217. In my opinion, Lovshin anticipated claim 3 of the '462 patent. Claim 3 depends from claim 2 and recites, "[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection."

218. Lovshin disclosed that the dose of NN9535 (semaglutide) to be administered to a patient is "0.1–1.6 mg once weekly," given by "subcutaneous injection" to treat type 2 diabetes. Ex. 1012 (Lovshin) at 2. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

219. Lovshin therefore anticipated claim 3 of the '462 patent.

C. GROUND 3: CLAIMS 1-10 OF THE '462 PATENT WOULD HAVE BEEN OBVIOUS OVER WO421

220. As described below, in my opinion claims 1-10 of the '462 patent would have been obvious over WO421.

1. Claim 1 would have been obvious over WO '421

221. Independent claim 1 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 over WO421.

a. Teachings of WO421

222. The teachings of WO '421 are detailed above in paragraphs 106-111.

b. Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

223. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, WO421, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

224. To begin, skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance. *See* Lund (Ex. 1035) at 5. As I discussed previously, in my opinion, "[a]method for treating type 2 diabetes," should be interpreted broadly. *See supra* ¶¶ 56-60. Based on the teachings of WO421, skilled artisans would have known that WO421 disclosed methods for treating and/or preventing type 2 diabetes by administering a GLP-1 receptor agonist, such as semaglutide. *See, e.g.,* Ex. 1011 (WO421) at 2:4-9, 34:20-22 ("Preferred examples of GLP-1 receptor agonists (GLP-1 analogues) of this

invention are exenatide, exenatide LAR, liraglutide, taspoglutide, *semaglutide*, albiglutide, lixisenatide and dulaglutide.") (emphasis added), claim 17.

225. Moreover, a skilled artisan would have known from WO421 that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)." *Id.* at 44:13. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide.

226. Skilled artisans would have been motivated to look to the teachings in the art with respect to using semaglutide to treat type 2 diabetes. As taught in the art, Novo Nordisk was actively investigating semaglutide in phase I and phase II studies. For example, in 2009, Lovshin disclosed that semaglutide was under clinical investigation in phase I-II studies. Ex. 1012 (Lovshin) at 5. In 2011, Lund confirmed this disclosing, "[s]o 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)." Ex. 1035 (Lund) at 7-8; *see also id.* at Table 1.

227. A skilled artisan would also have known that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg

semaglutide, the same dose range disclosed in WO421. Ex. 1012 (Lovshin) at 2, Table 1; Ex. 1011 (WO421) at 44:13. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Ex. 1047 (Tamimi) at 3-4; Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6; Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

228. The skilled artisan would have understood that the doses (or exposures) tested in phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See supra* paragraphs 65-74; Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1; Ex. 1084 (ICH 2001) at 5-8).

229. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would be suboptimal doses, in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

230. Indeed, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies and the skilled artisan would be motivated with a reasonable expectation of success to optimize the weekly dose to 1.0 mg for treating type 2 diabetes.

231. In particular, a skilled artisan would have been aware that the completed NCT657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. Ex. 1013 (NCT657) at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose of semaglutide and would have had a reasonable expectation of success in doing so.

232. Based on the doses that Novo Nordisk selected to test in the NCT657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective in treating type 2 diabetes. As discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., *in vitro* and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See* Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were supported by a breadth of internal preclinical studies and knowledge about semaglutide.

233. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum

response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have reasonably expected that the 1.6 mg dose was chosen as a dose expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

234. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. Indeed, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.,* Ex. 1039 (Victoza label) at 2 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose "to reduce gastrointestinal symptoms during initial titration."). Thus, a skilled artisan would be motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

235. Indeed, the NCT773 phase I study, assessing the safety and tolerability of semaglutide, would provide further motivation to optimize to a weekly dose such as 1.0 mg semaglutide because in that study, the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT657 phase II study was completed in February 2009 (Ex. 1013 (NCT657) at 15), which was the same month that the NCT773 phase I study was just starting. *See* Ex. 1014 (NCT773) at 7 (disclosing a "Study Start Date" of "February 2009.").

236. A skilled artisan would have known that the highest doses tested in the NCT773 phase I study differed from the highest doses tested in the NCT657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the NCT773 phase I study instead tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and *1.2 mg* semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. *Compare* Ex. 1013 (NCT657) at 15-16 *with* Ex. 1014 (NCT773) at 7. In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a 1.2 mg dose implies that Novo Nordisk was fine tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT657 phase II study.

237. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further reasonable expectation that the once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

238. Moreover, because liraglutide was shown to exhibit the classic sigmoidal dose/response profile for lowering HbA_{1c}, (*see* Ex. 1038 (Seino) at 4, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship with semaglutide for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Ex. 1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

239. Accordingly, claim 1 of the '462 patent would have been obvious to a skilled artisan over WO421.

2. Claim 2 would have been obvious over WO '421

240. In my opinion, claim 2 of the '462 patent would have been obvious over WO421. Claim 2 depends from claim 1 and recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration."

241. WO421 disclosed that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)" to treat type 2 diabetes. WO421 at 43:13. In my opinion, skilled artisans would have known that subcutaneous injection is a type of parenteral administration. *See, e.g.,* Ex. 1015 (WO537) at 35:15-16 ("Parenteral administration may be performed by subcutaneous . . . injection.").

242. Accordingly, claim 2 of the '462 patent would have been obvious to a skilled artisan over WO421.

3. Claim 3 would have been obvious over WO '421

243. In my opinion, claim 3 of the '462 patent would have been obvious over WO421. Claim 3 depends from claim 2 and recites, "[t]he method according to claim 2, wherein the solution is administered by subcutaneous injection."

244. WO421 disclosed that "[s]emaglutide is administered once weekly by subcutaneous injection (0.1-1.6 mg)" to treat type 2 diabetes. WO421 at 43:13. In my opinion, skilled artisans would have known that a subcutaneous injection is necessarily a solution.

245. Accordingly, claim 3 of the ’462 patent would have been obvious to a skilled artisan over WO421.

4. Claims 4-10 would have been obvious over WO ’421 considering the ’424 publication

246. As I described above, it is my opinion that claims 1-3 of the ’462 patent would have been obvious over WO421. It is my understanding that Mylan’s formulation expert, Dr. Dalby, is submitting an expert declaration and providing an opinion that claims 4-10 of the ’462 patent would have been obvious over WO421 considering the ’424 publication. It is therefore my opinion that claims 4-10 of the ’462 patent would have been obvious over WO421 considering the ’424 publication for the reasons discussed above and for the reasons discussed by Dr. Dalby.

D. GROUND 4: CLAIMS 1-10 OF THE ’462 PATENT WOULD HAVE BEEN OBVIOUS OVER WO537 CONSIDERING LOVSHIN

247. As described below, in my opinion claims 1-10 of the ’462 patent would have been obvious over WO537 considering Lovshin. It is my understanding that Mylan’s formulation expert, Dr. Dalby, is submitting an expert declaration and providing an opinion that claims 4-10 of the ’462 patent would have been obvious over WO537 considering Lovshin.

1. Claim 1 would have been obvious over WO537 considering Lovshin

248. Independent claim 1 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 over WO537 considering Lovshin.

a. Teachings of WO537 and Lovshin

249. The teachings of WO537 are detailed above in paragraphs 116-120.

250. The teachings of Lovshin are detailed above in paragraphs 112-115.

b. Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

251. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, WO537 in combination with Lovshin 2009, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

252. Skilled artisans would have known that Novo Nordisk was investigating a dose range of between 0.1-1.6 mg semaglutide once weekly to treat type 2 diabetes. As a result, skilled artisans would have engaged in routine optimization to determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide.

253. To begin, skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes because it allows for reduction in frequency of injections and improved compliance. Lund (Ex. 1035) at 5. As I discussed previously, in my opinion, "[a]method for treating type 2 diabetes," should be interpreted broadly. *See supra* ¶¶ 56-60. Based on the teachings of WO537, a skilled artisan would have known that semaglutide could be used in "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." Ex. 1015 (WO537) at 23:24-24:3. Example 4 of WO537 disclosed the structure of semaglutide. *Id.* at 48:4-8; *see also id.* at 73:17-75:10. WO537 also disclosed that the disclosed formulations could be administered parenterally, such as by subcutaneous injection. *Id.* at 35:15-16 ("Parenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe.").

254. Skilled artisans would have been motivated to look to teachings in the art with respect to using semaglutide to treat type 2 diabetes. As taught in the art, Novo Nordisk was actively investigating semaglutide in phase I and phase II studies. For example, in 2009, Lovshin disclosed that semaglutide was under clinical investigation in phase I-II studies. Ex. 1012 (Lovshin) at 5. In 2011, Lund confirmed this disclosing, "[s]o 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)." Ex. 1035 (Lund) at 7-8; *see also id.* at Table 1.

255. A skilled artisan would also have known from Lovshin that the dose range being investigated by Novo Nordisk was a once weekly dose of between 0.1-1.6 mg semaglutide. Ex. 1012 (Lovshin) at 2, Table 1. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Ex. 1047 (Tamimi) at 3-4; Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6; Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

256. The skilled artisan would have understood that the doses (or exposures) tested in phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been

subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human patients. *See supra* paragraphs 65-74; Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1; Ex. 1084 (ICH 2001) at 5-8.

257. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would be suboptimal doses, in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

258. Indeed, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies, which would confirm that a skilled artisan would be motivated with a reasonable expectation of success to optimize the weekly dose to 1.0 mg for treating type 2 diabetes.

259. In particular, a skilled artisan would have been aware that the completed NCT657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. Ex. 1013

(NCT657) at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides further confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with a 1.0 mg weekly dose of semaglutide and would have had a reasonable expectation of success in doing so.

260. Based on the doses that Novo Nordisk selected to test in the NCT657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective in treating type 2 diabetes. As discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., in vitro and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See* Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were supported by a breadth of internal preclinical studies and knowledge about semaglutide. *See supra* paragraphs 65-74.

261. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1, 0.2, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-response curve. A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have understood that the 1.6 mg dose was expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

262. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose would likely result in unwanted side effects, such as gastrointestinal problems. Indeed, other GLP-1-receptor agonists, such as the similarly structured liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.,* Ex. 1039 (Victoza label) at 2

(allowing for titration of liraglutide from 0.6 to 1.2 mg dose "to reduce gastrointestinal symptoms during initial titration."). Thus, a skilled artisan would be motivated to look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

263. Indeed, the NCT773 phase I study, assessing the safety and tolerability of semaglutide, would provide further motivation to optimize to a weekly dose such as 1.0 mg semaglutide because in that study, the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT657 phase II study was completed in February 2009 (Ex. 1013 (NCT657) at 15), which was the same month that the NCT773 phase I study was just starting. *See* Ex. 1014 (NCT773) at 7 (disclosing a "Study Start Date" of "February 2009.").

264. A skilled artisan would have known that the highest doses tested in the NCT773 phase I study differed from the highest doses tested in the NCT657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the NCT773 phase I study instead tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and *1.2 mg* semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. *Compare* Ex. 1013 (NCT657) at 15-16 *with* Ex. 1014 (NCT773) at 7.

In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a 1.2 mg dose implies that Novo Nordisk was fine tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT657 phase II study.

265. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing an even further reasonable expectation that the once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

266. Moreover, because liraglutide was shown to exhibit the classic, sigmoidal dose/response profile for lowering HbA_{1c}, (*see* Ex. 1038 (Seino) at 4, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship with semaglutide for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Ex. 1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures

further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

267. Accordingly, claim 1 of the '462 patent would have been obvious to a skilled artisan over WO537 considering Lovshin.

2. Claim 2 would have been obvious over WO537 considering Lovshin

268. In my opinion, claim 2 of the '462 patent would have been obvious over WO537 considering Lovshin. Claim 2 depends from claim 1 and recites, "[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration."

269. WO537 disclosed, "[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe." Ex. 1015 (WO537) at 35:15-16. Thus, skilled artisans would have known that subcutaneous injection is a type of parenteral administration.

270. Accordingly, claim 2 of the '462 patent would have been obvious to a skilled artisan over WO537 considering Lovshin.

3. Claim 3 would have been obvious over WO537 considering Lovshin

271. In my opinion, claim 3 of the '462 patent would have been obvious over WO537 considering Lovshin. Claim 3 depends from claim 2 and recites, "[t]he

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

272. WO537 disclosed, "[p]arenteral administration may be performed by subcutaneous, intramuscular, intraperitoneal or intravenous injection by means of a syringe, optionally a pen-like syringe." Ex. 1015 (WO537) at 35:15-16. In my opinion, skilled artisans would have known that subcutaneous injection is necessarily a solution.

273. Accordingly, claim 3 of the '462 patent would have been obvious to a skilled artisan over WO537 considering Lovshin.

4. Claims 4-10 would have been obvious over WO537 considering Lovshin

274. As I described above, it is my opinion that claims 1-3 of the '462 patent would have been obvious over WO537 considering Lovshin. It is my understanding that Mylan's formulation expert, Dr. Dalby, is submitting an expert declaration and providing an opinion that claims 4-10 of the '462 patent would have been obvious over WO537 considering Lovshin. It is therefore my opinion that claims 4-10 of the '462 patent would have been obvious over WO537 considering Lovshin for the reasons discussed above and for the reasons discussed by Dr. Dalby.

E. GROUND 5: CLAIMS 1-10 OF THE '462 PATENT WOULD HAVE BEEN OBVIOUS OVER NCT657 AND NCT773

275. As described below, in my opinion claims 1-10 of the '462 patent would have been obvious over NCT657 and NCT773. It is my understanding that Mylan's formulation expert, Dr. Dalby, is submitting an expert declaration and providing an opinion that claims 4-10 of the '462 patent would have been obvious over NCT657 and NCT773 in view of the '424 publication.

1. Claim 1 would have been obvious over NCT657 and NCT773

276. Independent claim 1 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 over NCT657 and NCT773.

a. Teachings of NCT657 and NCT773

277. The teachings of NCT657 are detailed above in paragraphs 121-125.

278. The teachings of NCT773 are detailed above in paragraphs 126-130.

b. Skilled artisans would have been motivated to pursue, with a reasonable expectation of success, the treatment of type 2 diabetes with a once weekly 1.0 mg dose of semaglutide

279. In my opinion, in view of the state of the art and a skilled artisan's general knowledge before July 1, 2012, in particular, NCT657 and NCT773, skilled artisans would have been motivated to optimize the once weekly dose of semaglutide

to treat type 2 diabetes patients with a once weekly 1.0 mg dose of semaglutide and would have had a reasonable expectation of success in doing so.

280. To begin, skilled artisans would have been motivated to use once weekly semaglutide as a treatment for type 2 diabetes, because it allows for reduction in frequency of injections and improved compliance. Lund (Ex. 1035) at 5. As I discussed previously, in my opinion, "[a]method for treating type 2 diabetes," should be interpreted broadly. *See supra* ¶¶ 56-60. As taught in the art, Novo Nordisk was actively investigating semaglutide in phase I and phase II studies. For example, in 2009, Lovshin disclosed that semaglutide was under clinical investigation in phase I-II studies. Ex. 1012 (Lovshin) at 5. In 2011, Lund confirmed this disclosing, "[s]o 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)." Ex. 1035 (Lund) at 7-8; *see also id.* at Table 1.

281. Skilled artisans would have known that Novo Nordisk was investigating a dose range of between 0.1-1.6 mg semaglutide once weekly to treat type 2 diabetes in a phase II study and a dose range of 0.1-1.2 mg semaglutide once weekly in phase I study. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7-8. As a result, skilled artisans would have engaged in routine optimization to

determine an effective dose of semaglutide that produces minimal side effects, which were well-known to be caused by GLP-1 receptor agonists, such as semaglutide.

282. In my opinion, a skilled artisan would have been motivated to pursue a 1.0 mg weekly dose of semaglutide as a treatment for type 2 diabetes because it would be understood that certain doses being tested in phase I and II studies within the 0.1-1.6 mg range would be more effective than others. A skilled artisan would understand that the phase I and II studies would be dose-ranging studies, in which Novo Nordisk would have selected doses to test to provide a dose-response curve to determine the suboptimal doses and the optimal doses, the most effective doses with the least side effects. *See* Ex. 1047 (Tamimi) at 3-4; Ex. 1048 (FDA Exposure Response 2003) at 7; Ex. 1049 (ICH 1994) at 1-2, 4, 6; Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

283. The skilled artisan would have understood that the doses tested in phase I and II studies had already been tested in preclinical models and would be safe for human administration. Moreover, the skilled artisan would have understood that the doses tested in phase I and phase II studies would have been subject to the scrutiny of a human subjects institutional review board before testing began. The skilled artisan would have understood that for the studies to proceed, there was a scientific rationale and support for those doses being both safe and efficacious in human

patients. *See supra* paragraphs 65-74; Ex. 1047 (Tamimi) at 3; Ex. 1066 (Knudsen 2010b) at 1; Ex. 1084 (ICH 2001) at 5-8.

284. In my opinion, a skilled artisan would reasonably expect that the doses on the lower end of the range (e.g., ~0.1 mg doses) would be suboptimal doses, in contrast to doses on the higher end of the range (e.g., ~1.6 mg doses), which would likely be found on the plateau of the dose ranging curve, providing the maximum beneficial effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2.

285. Indeed, by the priority date of July 1, 2012, a skilled artisan would have been aware of the doses that Novo Nordisk chose to test in the phase I and phase II dose ranging studies, and a skilled artisan would be motivated with a reasonable expectation of success to optimize the weekly dose of semaglutide to 1.0 mg for treating type 2 diabetes.

286. In particular, a skilled artisan would have been aware that the completed NCT657 phase II randomized-controlled clinical trial comparing semaglutide with placebo and liraglutide included six experimental arms (A-F), that consisted of subcutaneous injection once weekly doses of semaglutide at 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, 0.8 mg with titration, and 1.6 mg with titration. NCT657 at 15-16. That these were the doses tested in the phase II dose-ranging study by Novo Nordisk provides confirmation that a skilled artisan would have been motivated to optimize the once weekly dose of semaglutide to treat type 2 diabetes patients with

a 1.0 mg weekly dose and would have had a reasonable expectation of success in doing so.

287. Based on the doses that Novo Nordisk selected to test in the NCT657 phase II study, 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, a skilled artisan would have had a reasonable expectation of success that doses of at least between 0.8 to 1.6 mg semaglutide, such as 1.0 mg, would be effective in treating type 2 diabetes. As discussed above, a skilled artisan would have been aware that the purpose of a phase II study would be to evaluate a variety of doses, including suboptimal doses and maximum effective doses to provide a dose-response curve and determine the optimal doses. Further, a skilled artisan would also understand that prior to undergoing any phase I or phase II human studies, Novo Nordisk would have collected a substantial amount of pre-clinical data (i.e., in vitro and healthy and diseased animal models) related to the pharmacokinetics and pharmacodynamics of semaglutide. *See, e.g.*, Ex. 1066 (Knudsen 2010b) at 1. Thus, a skilled artisan would have understood that the doses selected in Novo Nordisk's dose-ranging study were supported by a breadth of internal preclinical studies and knowledge about semaglutide. *See supra* paragraphs 65-74.

288. In my opinion, a skilled artisan would have further understood that the lower doses, such as 0.1 mg, 0.2 mg, and 0.4 mg, would have been selected by Novo Nordisk to provide information about the suboptimal semaglutide doses on the dose-

response curve. A skilled artisan would have also understood that higher doses, such as the 0.8 mg and 1.6 mg doses, were chosen by Novo Nordisk to evaluate the maximum response of semaglutide on the dose-response curve. Moreover, a skilled artisan would have reasonably expected that the 1.6 mg dose was chosen as a dose expected to be on the plateau of the dose-response curve, such that it would provide a maximum effect. *See* Ex. 1045 (Shargel) at 81-82, Figs. 19-1 and 19-2. Thus, a skilled artisan would have been motivated to optimize the weekly dose of semaglutide to between 0.8 mg and 1.6 mg and would have understood that the disclosed range included a discrete number of dosing steps, typically proceeding in 0.1 mg increments. A skilled artisan would have been motivated to try a 1.0 mg dose with a reasonable expectation that it would be effective in treating type-2 diabetes because it would have been one of seven 0.1 mg dose increments to test between 0.8 mg to 1.6 mg.

289. Moreover, a skilled artisan would be further motivated to optimize to a 1.0 mg dose within the 0.8 mg to 1.6 mg range because the 1.6 mg dose, would likely result in unwanted side effects, such as gastrointestinal problems. Indeed, other GLP-1-receptor agonists, such as the similarly structured, liraglutide, produced gastrointestinal problems at higher doses. *See, e.g.,* Ex. 1039 (Victoza label) at 2 (allowing for titration of liraglutide from 0.6 to 1.2 mg dose "to reduce gastrointestinal symptoms during initial titration."). Thus, a skilled artisan would be

motivated look to optimize to a dose below the highest 1.6 mg dose tested in the phase II study, to provide effective treatment without unwanted side effects.

290. Indeed, the NCT773 phase I study, assessing the safety and tolerability of semaglutide, would provide further motivation to optimize to a weekly dose such as 1.0 mg semaglutide because in that study, the highest dose tested was 1.2 mg, not 1.6 mg semaglutide. By the earliest alleged priority date of July 1, 2012, a skilled artisan would have known that the NCT657 phase II study was completed in February 2009 (Ex. 1013 (NCT657) at 15), which was the same month that the NCT773 phase I study was just starting. *See* Ex. 1014 (NCT773) at 7 (disclosing a "Study Start Date" of "February 2009.").

291. A skilled artisan would have known that the highest doses tested in the NCT773 phase I study differed from the highest doses tested in the NCT657 phase II study. In particular, instead of testing the same once weekly doses that were tested in the NCT657 phase II study, i.e., 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and 1.6 mg semaglutide, the NCT773 phase I study instead tested 0.1 mg, 0.2 mg, 0.4 mg, 0.8 mg, and *1.2 mg* semaglutide once weekly, effectively reducing the 1.6 mg semaglutide dose, the highest dose tested in the phase II study, to 1.2 mg semaglutide. *Compare* Ex. 1013 (NCT657) at 15-16 *with* Ex. 1014 (NCT773) at 7. In my opinion, a skilled artisan would have understood that this change from using a 1.6 mg dose to using a lower 1.2 mg dose implies that Novo Nordisk was fine

tuning its clinical protocol, perhaps based on data collected from the earlier performed NCT657 phase II study.

292. In my opinion, this would further narrow the range of potential doses from between 0.8 mg to 1.2 mg semaglutide providing even further reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

293. Moreover, because liraglutide was shown to exhibit the classic, sigmoidal dose/response profile for lowering HbA_{1c}, (*see* Ex. 1038 (Seino) at 4, Fig. 1), and because semaglutide is also a GLP-1 agonist with a similar structure and mechanism of action, a skilled artisan would have a strong scientific basis to expect a similar dose response relationship for lowering HbA_{1c}. The animal and human studies with liraglutide, the basic understanding of the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists, and the appreciation that several other agents were in development for once weekly dosing (e.g., Ex. 1012 (Lovshin) at Table 1) would have led a skilled artisan to expect consistency in responses between liraglutide and semaglutide on lowering glucose and HbA_{1c} in diabetic patients leading to progressive reductions of these biomarkers from lower to higher doses until reaching a plateau. In my opinion, these disclosures further supported the skilled artisan's reasonable expectation that a once weekly 1.0 mg semaglutide dose would be successful for treating type 2 diabetes.

294. Accordingly, claim 1 of the ’462 patent would have been obvious to a skilled artisan over NCT657 and NCT773.

2. Claim 2 would have been obvious over NCT657 and NCT773

295. In my opinion, claim 2 of the ’462 patent would have been obvious over NCT657 and NCT773. Claim 2 depends from claim 1 and recites, “[t]he method according to claim 1, wherein the semaglutide is administered by parenteral administration.”

296. Both NCT657 and NCT773 disclosed that semaglutide in the phase II and phase I trials, respectively, were administered as a subcutaneous injection. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. In my opinion, skilled artisans would have known that subcutaneous injection is a type of parenteral administration. *See, e.g.,* Ex. 1015 (WO537) at 35:15-16 (“Parenteral administration may be performed by subcutaneous . . . injection.”).

297. Accordingly, claim 2 of the ’462 patent would have been obvious to a skilled artisan over NCT657 and NCT773.

3. Claim 3 would have been obvious over NCT657 and NCT773

298. In my opinion, claim 3 of the ’462 patent would have been obvious over NCT657 and NCT773. Claim 3 depends from claim 2 and recites, “[t]he method

according to claim 2, wherein the solution is administered by subcutaneous injection."

299. Both NCT657 and NCT773 disclosed that semaglutide in the phase II and phase I trials, respectively, were administered as a subcutaneous injection. *See* Ex. 1013 (NCT657) at 15-16; Ex. 1014 (NCT773) at 7. In my opinion, skilled artisans would have known that subcutaneous injection is necessarily a solution.

300. Accordingly, claim 3 of the '462 patent would have been obvious to a skilled artisan over NCT657 and NCT773.

4. Claims 4-10 would have been obvious over NCT657, NCT773, and the '424 publication

301. As I described above, it is my opinion that claims 1-3 of the '462 patent would have been obvious over NCT657 and NCT773. It is my understanding that Mylan's formulation expert, Dr. Dalby, is submitting an expert declaration and providing an opinion that claims 4-10 of the '462 patent would have been obvious over NCT657, NCT773, and the '424 publication. It is therefore my opinion that claims 4-10 of the '462 patent would have been obvious over NCT657, NCT773, and the '424 publication for the reasons discussed above and for the reasons discussed by Dr. Dalby.

F. NO SECONDARY CONSIDERATIONS OVERCOME *PRIMA FACIE* OBVIOUSNESS OF THE CLAIMED ALLEGED INVENTIONS

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

1. No unexpected results

303. Neither the '462 patent (Ex. 1001) nor its prosecution history (Ex. 1002) disclosed unexpected results regarding the claimed method. There is also no disclosure or suggestion that the claimed 1.0 mg once weekly dose of semaglutide was somehow "critical." As I discussed above, the prior art demonstrates the claimed method for treating type 2 diabetes comprising administering once weekly semaglutide in an amount of 1.0 mg would have been obvious.

2. No long-felt, unmet need or skepticism

304. Patent Owner may assert that there was a long-felt but unmet need for a once weekly GLP-1-derived treatment for treating type 2 diabetes. In my opinion, the prior art confirms that such a need did not exist. As I discussed above, once weekly GLP-1 receptor agonists existed in the prior art before the priority date. Ex. 1012 (Lovshin) at 2, Table 1.

305. Further, Patent Owner may assert that there was skepticism of the claimed method of treating type 2 diabetes with semaglutide. As I discussed above,

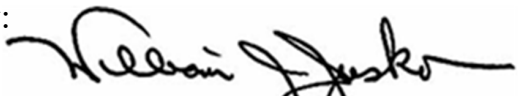
the prior art provided motivation and expectations related to dosing and the use of semaglutide. In my opinion, assertions of skepticism would not outweigh the obviousness detailed above.

X. CONCLUSION

306. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

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

Dated: 3/15/2023

By: 

William J. Jusko, PhD.

EXHIBIT A

EXHIBIT A

Exhibit No.	Description
1001	U.S. Patent No. 10,335,462
1002	U.S. Patent No. 10,335,462 file history excerpts
1011	International Patent App. Pub. No. WO 2011/138421
1012	Lovshin, *Incretin-Based Therapies for Type 2 Diabetes Mellitus*, 5 NATURE REVIEWS ENDOCRINOLOGY 262 (2009)
1013	Clinical Trial No. NCT00696657
1014	Clinical Trial No. NCT00851773
1015	International Patent App. Pub. No. WO 2006/097537
1016	U.S. Patent App. Pub. No. US2007/0010424
1017	U.S. Patent No. 5,512,549
1019	Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983)
1922	Drab, *Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects*, 30 PHARMACOTHERAPY 609 (2010)
1027	Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987)
1032	Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 J. MED. CHEMISTRY 4128 (2004)
1035	Lund, *Emerging GLP-1Receptor Agonists*, 16 EXPERT OPINION ON EMERGING DRUGS 607 (2011)

Exhibit No.	Description
1036	Mojsov, *Insulinotropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas*, 79 J. CLIN. INVEST. 616 (1987)
1038	Seino, *Dose-Dependent Improvement in Glycemia with Once-Daily Liraglutide without Hypoglycemia or Weight Gain: A Double-Blind, Randomized, Controlled Trial in Japanese Patients with Type 2 Diabetes*, 81 DIABETES RSCH. & CLINICAL PRACTICE 161 (2008)
1039	*Victoza*, PHYSICIANS' DESK REFERENCE (65th ed. 2010)
1042	International Patent App. Pub. No. WO 91/11457
1043	U.S. Patent App. Pub. No. 2004/0102486
1044	Rohatagi, *Model-Based Development of a PPARγ Agonist, Rivoglitazone, to Aid Dose Selection and Optimize Clinical Trial Designs*, 48 J. CLIN. PHARM. 1420 (2008)
1045	Shargel, APPLIED BIOPHARMACEUTICS & PHARMACOKINETICS (5th ed. 2005)
1046	Yun, *Pharmacokinetic and Pharmacodynamic Modelling of the Effects of Glimepiride on Insulin Secretion and Glucose Lowering in Healthy Humans*, 31 J. CLIN. PHARM. & THER. 469 (2006)
1047	Tamimi, *Drug Development: From Concept to Marketing!*, 113 NEPHRON CLIN PRACT c125 (2009)
1048	FDA Guidance for Industry, *Exposure-Response Relationships - Study Design, Data, Analysis, and Regulatory Applications* (Apr. 2003)
1049	*International Conference on Harmonisation; Dose-Response Information to Support Drug Registration; Guideline; Availability*, 59 Fed. Reg. 55972 (Nov. 9, 1994) ("ICH 1994")

Exhibit No.	Description
1050	Garber, *Efficacy of Metformin in Type II Diabetes: Results of a Double-Blind, Placebo-Controlled, Dose-Response Trial*, 102 AM. J. MED. 491 (1997)
1051	Landersdorfer, *Pharmacokinetic/Pharmacodynamic Modelling in Diabetes Mellitus*, 47(7) CLIN PHARMACOKINET 417 (2008)
1052	Madsbad, *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)
1053	Møller, *Mechanism-Based Population Modelling for Assessment of L-Cell Function Based on Total GLP-1 Response Following an Oral Glucose Tolerance Test*, 38 J. PHARMACOKINET PHARMACODYN 713 (2011)
1054	Landersdorfer, *Mechanism-Based Population Pharmacokinetic Modelling in Diabetes: Vildagliptin as a Tight Binding Inhibitor and Substrate of Dipeptidyl Peptidase IV*, 73 Br J Clin Pharmacol 391 (2011) ("Landersdorfer 2011")
1055	Landersdorfer, *Mechanism-Based Population Modelling of the Effects of Vildagliptin on GLP-1, Glucose and Insulin in Patients with Type 2 Diabetes*, 73 BR J CLIN PHARMACOL 373 (2011) ("Landersdorfer 2011b")
1057	International Patent App. Pub. No. WO 2011/073328
1058	Blonde, *Comparison of Liraglutide Versus Other Incretin-Related Anti-Hyperglycaemic Agents*, 14 (suppl. 2) DIABETES, OBESITY & METABOLISM 20 (2012)
1059	Murphy, *Review of the Safety and Efficacy of Exenatide Once Weekly for the Treatment of Type 2 Diabetes Mellitus*, 46 ANN PHARMACOTHER 812 (2012)
1060	International Patent App. Pub. No. WO 2011/058193

Exhibit No.	Description
1061	U.S. Patent App. Pub. No. 2011/0166321
1062	Zarin, *The ClinicalTrials.gov Results Database—Update and Key Issues*, 364 NEW ENGL. J. MED. 852 (2011)
1063	Kirillova, *Results and Outcome Reporting in ClinicalTrials.gov, What Makes it Happen?*, 7(6) PLOS ONE 1 (2012)
1064	Monami, *Effects of Glucagon-Like Peptide-1 Receptor Agonists on Body Weight: A Meta-Analysis*, 2012 EXPERIMENTAL DIABETES RSCH. 1 (2012)
1065	Tasneem, *The Database for Aggregate Analysis of ClinicalTrials.gov (AACT) and Subsequent Regrouping by Clinical Specialty*, 7(3) PLOS ONE 1(2012)
1066	Knudsen, *Liraglutide: The Therapeutic Promise from Animal Models*, 64(suppl 167) INT J CLIN PRACT 4 (2010) ("Knudsen 2010b")
1078	U.S. Patent App. Pub. No. 2004/0102486
1084	EMA, *ICH Topic S 7 A Safety Pharmacology Studies for Human Pharmaceuticals* (June 2001)