UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

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Case No. IPR2023-00722

Patent No. 8,536,122

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**DECLARATION OF JOHN BANTLE, M.D., IN SUPPORT OF PETITION FOR *INTER PARTES* REVIEW OF U.S. PATENT NO. 8,536,122**

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*1. A skilled artisan would have been motivated by Knudsen 2004, the Knudsen patent, Dong, or Bridon to arrive at the invention claimed in claim 15 of the '122 patent* ..... 59

*2. A skilled artisan would have had a reasonable expectation of success of treating hyperglycemia and/or type 2 diabetes in a subject with an effective amount of a GLP-1(7-37) analog, including semaglutide, recited in claim 1* ..... 61

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## TABLE OF ABBREVIATIONS

| Full Name of Cited Reference | Abbreviation |
|---|---|
| U.S. Patent No. 8,536,122 | '122 patent |
| U.S. Patent No. 8,129,343 | '343 patent |
| U.S. Patent No. 5,512,549 | '549 patent |
| U.S. Patent No. 6,284,727 | '727 patent |
| Baggio, *Glucagon-like Peptide 1 and Glucagon-like Peptide 2*, 18 BEST PRAC. & RSCH. CLINICAL ENDOCRINOLOGY & METABOLISM 531 (2004) | Baggio 2004b |
| Banting, *The Internal Secretion of the Pancreas,* 7 J. LAB. CLINICAL MED. 251 (1922) | Banting |
| Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983) | Bell |
| U.S. Patent No. 6,514,500 | Bridon |
| Dong, *Glucagon-Like Peptide-1 Analogs with Significantly Improved in vivo Activity*, in PEPTIDES: THE WAVE OF THE FUTURE (Michal Lebl et al. eds., 2001) | Dong |
| Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003) | Drucker 2003 |
| Giannoukakis, *CJC-1131 ConjuChem*, 4(10) CURRENT OP. IN INVESTIGATIONAL DRUGS 1245 (2003) | Giannoukakis |
| Gutniak, *Antidiabetogenic Effect of Glucagon-Like Peptide-1 (7-36)Amide in Normal Subjects and Patients with Diabetes Mellitus*, 326 NEW ENG. J. MED. 1316 (1992) | Gutniak |
| HARRISON'S PRINCIPLES OF INTERNAL MED., Chapter 333 (Braunwald et al. eds. 15th ed. 2001) | Harrison's |
| Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987) | Holst |
| Holst, *The Incretin Approach for Diabetes Treatment: Modulation of Islet Hormone Release by GLP-1 Agonism*, 53 (suppl. 3) DIABETES S197 (2004) | Holst 2004 |

**TABLE OF ABBREVIATIONS**
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| Full Name of Cited Reference | Abbreviation |
|---|---|
| Holst, *Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus*, 4 CURRENT OP. IN PHARM. 589 (2004) | Holst 2004b |
| Knudsen, *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26(7) DRUGS OF THE FUTURE (2001) | Knudsen 2001 |
| Knudsen, *Glucagon-Like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47(17) J. MED. CHEM. 4128 (2004) | Knudsen 2004 |
| U.S. Patent No. 6,268,343 | Knudsen patent |
| Madsbad, *Improved Glycemic Control with No Weight Increase in Patients with Type 2 Diabetes After Once-Daily Treatment with the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211): A 12-Week, Double-Blind, Randomized, Controlled Trial*, 27 DIABETES CARE 1335 (2004) | 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. CLINICAL INVESTIGATION 616 (1987) | Mojsov |
| Nauck, *Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36 amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients*, 36 DIABETOLOGIA 741 (1993) | Nauck |
| Ørskov, *Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7–36 Amide and Glucagonlike Peptide-1 7–37 in Healthy Subjects are Indistinguishable*, 42 DIABETES 658 (1993) | Orskov |
| Polonsky, *What's So Tough About Taking Insulin? Addressing the Problem of Psychological Insulin Resistance in Type 2 Diabetes*, 22(3) CLINICAL DIABETES 147 (2004) | Polonsky |
| WO 91/11457 | WO457 |

## TABLE OF ABBREVIATIONS
(continued)

| Full Name of Cited Reference | Abbreviation |
|---|---|
| WO 87/06941 | WO941 |

1. My name is John P. Bantle, M.D. I have been retained by Mylan Pharmaceuticals Inc. ("Mylan") to provide my expert opinions regarding the unpatentability of U.S. Patent No. 8,536,122 ("'122 patent") (Ex. 1001). I understand that Mylan intends to petition for *inter partes* review ("IPR") of the '122 patent, which is assigned to Novo Nordisk A/S. I also understand that, in the IPR petition, Mylan will request that the United States Patent and Trademark Office cancel claims 1-2, 4-11, 13, and 15 of the '122 patent as unpatentable. I submit this expert declaration to address and support Mylan's IPR petition for the '122 patent.

## I. QUALIFICATIONS AND BACKGROUND

### A. Education and Experience; Prior Testimony

2. I am a medical endocrinologist and Professor Emeritus of Medicine in the Division of Endocrinology and Diabetes, Department of Medicine, at the University of Minnesota. I have substantial experience in clinical research, treatment of patients, and academic publications in the field of the treatment of diabetes and related conditions.

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

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

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

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

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

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

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

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

9. My qualifications are further described on my *curriculum vitae*, attached as Exhibit 1027.

### B. Basis for Opinions and Materials Considered

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

### C. Retention and Compensation

11. Mylan retained me as a technical expert to provide various opinions about the '122 patent. I am being compensated at a rate of $400 per hour plus expenses for this work. My compensation is in no way tied to the outcome of this proceeding or to the content of this declaration, and it has not altered my opinions.

## II. SUMMARY OF OPINIONS

12. My opinions are limited to the treatment of diabetes with semaglutide, as claimed in the '122 patent. I present my opinions from the perspective of a POSA who is a medical doctor.

13. I understand that Mylan's experts Drs. Peter Flatt, Christopher Soares, and Paul Dalby are offering opinions that semaglutide falls within the scope of the GLP-1(7-37) derivatives claimed in claim 1 of the '122 patent, and that semaglutide would have been obvious to a POSA in view of the prior art. Specifically, I understand that there are three obviousness grounds presented:

(1) these claims would have been obvious over Knudsen 2004 in view of the Knudsen patent, Dong, and Bridon ("Ground 1");

(2) these claims would have been obvious over Knudsen 2001 in view of the Knudsen patent, Dong, and Bridon ("Ground 2"); and

(3) these claims would have been obvious in view of common drug development principles ("Ground 3").

14. My opinions are limited to the treatment of diabetes with a GLP-1 derivative claimed in the '122 patent. My opinions are from the perspective of a medical doctor who would collaborate with other experts.

15. First, with respect to motivation as it relates to the development of the semaglutide peptide, I offer the opinion that a POSA would have been motivated to make a longer-acting GLP-1 peptide.

16. Second, it is my opinion that the dependent "method of treatment" limitations contained in claim 15 of the '122 patent would have been obvious on the same grounds that render claim 1 unpatentable.

17. These references, in view of the state of the art, would have motivated a skilled artisan to treat hyperglycemia and/or type 2 diabetes in a subject who has diabetes, such as a human patient having diabetes, by administering to that patient an effective amount of semaglutide, with a reasonable expectation of success when doing so.

## III. LEGAL STANDARDS

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

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

20. I understand that my opinions regarding unpatentability are from the viewpoint of a person of ordinary skill in the art ("POSA") in the field of technology of the patent as of the patent's priority date.

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

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

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

## IV. PERSON OF ORDINARY SKILL IN THE ART

23. I understand my analysis is to be conducted from the perspective of a POSA as of the priority date of the '122 patent. I have also been informed by counsel that when defining a POSA, the following factors may be considered: (1) the educational level of the inventor; (2) the type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; and (5) sophistication of the technology and educational level of active workers in the field. Further, I understand a POSA is generally skilled in the relevant art (i.e., the subject matter claimed and described in the patent).

24. In my opinion, the following definition of a POSA applies to claims 1-2, 4-11, 13, and 15 of the '122 patent. The subject matter of the claims of the '122

patent falls within the medicinal chemical and pharmacological arts and encompasses the skills, education, and expertise of a team of individuals working together to develop and formulate GLP-1 analogues, as well as to use the GLP-1 analogues to treat patients having type-2 diabetes or related conditions. Such a team would have included individuals with an M.D., Pharm.D., or doctoral degree(s) in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, chemical engineering, biochemical engineering or related fields, with at least two years of experience developing therapeutic peptides or proteins, and experience with the development, design, manufacture, formulation, or administration of therapeutic peptides or proteins, and the literature concerning protein or peptide formulation and design or diabetes treatments.

25. Alternatively, the skilled artisan would be (1) a highly skilled scientist lacking an M.D., Pharm.D., or doctoral degree, but would have (2) (a) more than five years of experience in the area of developing therapeutic proteins or peptides and/or (b) experience with the development, design, manufacture, formulation, or administration of therapeutic agents for diabetes, and the literature concerning protein or peptide formulation and design or diabetes treatments. In either case, a higher educational level could substitute for some amount of the requisite experience.

26. Such a team also would have included persons with an appropriate level of skill in medicinal synthetic chemistry, including the synthesis and chemical modification of peptides or proteins.

27. With respect to the subject matter of claim 15 of the '122 patent, the team would have included an individual with an M.D. and experience treating patients having type 2 diabetes or related conditions.

28. With respect to claim 13 of the '122 patent, the team would have included an individual with a Ph.D. in chemistry, biochemistry, pharmaceutics, pharmaceutical sciences, chemical engineering, biochemical engineering, or related fields, with at least two years of experience in the formulation of therapeutic peptides or proteins.

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

30. As explained in this declaration and exemplified by the information provided in my CV, I met the qualifications of a skilled artisan for purposes of claim 15 as of the priority date of the '122 patent.

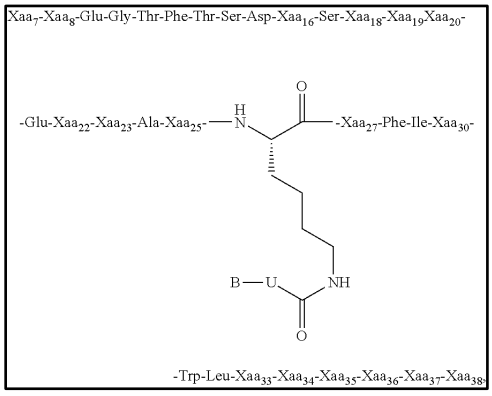
## V. THE '122 PATENT (EX. 1001) AND ITS CLAIMS

31. I have read the '122 patent, which is titled "Acylated GLP-1 compounds," including its claims, and relevant portions of the file histories of the '122 and '343 patents (Exs. 1003 and 1004, respectively).

32. I have assumed that the earliest priority date to which the claims of the '122 patent are entitled is March 18, 2005, which is the date recited on the face of the patent for foreign reference EP05102171, listed under "Foreign Application Priority Data." Therefore, references that pre-date March 18, 2005, are prior art. To the extent Patent Owner later asserts and/or proves that the claims are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

33. The '122 patent has one independent claim, which recites:

1. A compound of formula II (SEQ ID No. 3):



wherein

$Xaa_7$ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β-hydroxy-histidine, homohistidine, $N^{\alpha}$-acetyl-histidine, a-fluoromethyl-histidine, a-methyl-histidine, 3-pyridylalanine, 2-pyridylalanine, or 4-pyridylalanine;

$Xaa_8$ is Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

$Xaa_{16}$ is Val or Leu;

$Xaa_{18}$ is Ser, Lys, or Arg;

$Xaa_{19}$ is Tyr or Gln;

$Xaa_{20}$ is Leu or Met;

$Xaa_{22}$ is Gly, Glu, or Aib;

$Xaa_{23}$ is Gln, Glu, Lys, or Arg;

$Xaa_{25}$ is Ala or Val;

$Xaa_{27}$ is Glu or Leu;



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$Xaa_{30}$[2] is Ala, Glu, or Arg;

$Xaa_{33}$ is Val or Lys;

$Xaa_{34}$ is Lys, Glu, Asn, or Arg;

$Xaa_{35}$ is Gly or Aib;

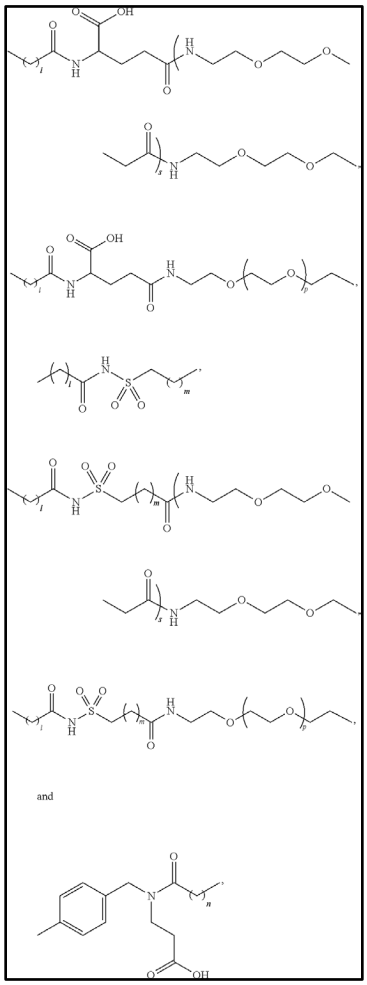
$Xaa_{36}$ is Arg, Gly, Lys, or is absent;

$Xaa_{37}$ is Gly, Ala, Glu, Pro, Lys, or is absent;

$Xaa_{38}$ is Lys, Ser, amide, or is absent; and

where U is a spacer selected from

[2] As corrected in a Certificate of Correction dated April 14, 2015.




where n is 12, 13, 14, 15, 16, 17, or 18,

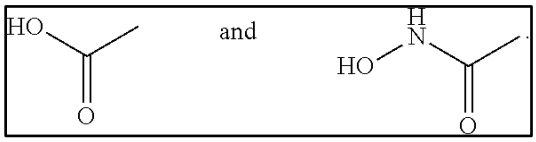
l is 12, 13, 14, 15, 16, 17, or 18,

m is 0, 1, 2, 3, 4, 5, or 6,

s is 0, 1, 2, or 3,

p is 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, or 23; and

where B is an acidic group selected from




34. Dependent claims 2–16 depend from claim 1, directly or indirectly, and are provided below.

35. Dependent claim 2 recites:

2. A GLP-1 analog according to claim 1, wherein

$Xaa_7$ is His or desamino-histidine;

$Xaa_8$ is Gly, Val, Leu, Ile, Lys or Aib;

$Xaa_{16}$ is Val;

$Xaa_{18}$ is Ser;

$Xaa_{19}$ is Tyr;

$Xaa_{20}$ is Leu;

$Xaa_{22}$ is Gly, Glu or Aib;

$Xaa_{23}$ is Gln or Glu;

$Xaa_{25}$ is Ala;

$Xaa_{27}$ is Glu;

$Xaa_{30}$ is Ala or Glu;

$Xaa_{33}$ is Val;

$Xaa_{34}$ is Lys or Arg;

$Xaa_{35}$ is Gly or Aib;

$Xaa_{36}$ is Arg or Lys

$Xaa_{37}$ is Gly, amide or is absent; and

$Xaa_{38}$ is absent.

36. Dependent claim 4 recites:

> 4. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises $Aib^8$ or $Gly^8$ in position 8 of the GLP-1(7-37) sequence.

37. Dependent claim 5 recites:

> 5. A GLP-1 analog according to claim 4, wherein said GLP-1 analog comprises $Aib^8$.

38. Dependent claim 6 recites:

> 6. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises no more than six amino acid residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

39. Dependent claim 7 recites:

> 7. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises no more than 3 amino acid

residues which have been exchanged, added or deleted as compared to GLP-1(7-37) (SEQ ID No. 1).

40. Dependent claim 8 recites:

8. A GLP-1 analog according to claim 1, wherein said GLP-1 analog comprises only one lysine residue.

41. Dependent claim 9 recites:

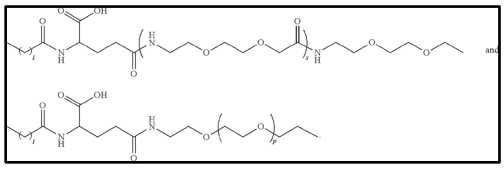
9. A GLP-1 analog according to claim 1, which is

$Aib^{8}$, $Arg^{34}$-GLP-1(7-37) or

$Aib^{8,22}$, $Arg^{34}$-GLP-1(7-37).

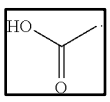
42. Dependent claim 10 recites:

10. A compound according to claim 1, wherein U is a spacer selected from



43. Dependent claim 11 recites:

11. A compound according to claim 10, wherein B is




44. Dependent claim 13 recites:

> 13. A pharmaceutical composition comprising a compound according to claim 1, and a pharmaceutically acceptable excipient.

45. Dependent claim 15 recites:

> 15. A method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 1.

## VI. CLAIM CONSTRUCTION

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

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

### A. Diabetes Generally

47. Insulin is a hormone produced and secreted by the pancreatic islets, Ex. 1109 (Harrison's) at 16, which is responsible for regulating the metabolism of blood sugar. Diabetes mellitus, commonly referred to as diabetes, is a metabolic disorder in which the body either fails to produce enough insulin or does not respond normally to insulin. *Id.* at 13. Thus, diabetes is characterized by elevated, and

sometimes abnormally and dangerously high, levels of glucose in the blood. *Id.* at 14.

48. There are three main types of diabetes: type 1, type 2, and gestational diabetes. Ex. 1109 (Harrison's) at 14. Type 1 diabetes, sometimes referred to as insulin-dependent diabetes, refers to a condition in which insulin production by the body is insufficient or absent. *Id.* at 16. Type 2 diabetes, sometimes referred to as non-insulin dependent diabetes (or NIDDM), involves both insulin resistance, which leads to an ineffective use of insulin by the body, and an inability to augment insulin secretion sufficiently to overcome that resistance. *Id.* at 18. The result is high blood glucose levels. Finally, gestational diabetes is a form of diabetes that affects pregnant women, which can be caused by either insulin resistance or a lack of insulin production. *Id.* at 14.

49. Diabetes is diagnosed by measuring a patient's blood glucose levels, testing glucose tolerance, and/or watching for signs and symptoms of diabetes. *Id.* at 15. Thus, diabetes may be diagnosed if the patient has a) symptoms of diabetes plus random blood glucose ≥11.1 mmol/L (200 mg/dL); or b) fasting plasma glucose ≥7.0 mmol/L (126 mg/dL); or c) two-hour plasma glucose ≥11.1 mmol/L (200 mg/dL) during an oral glucose tolerance test. *Id.* at 15, Table 333-2. If diabetes is not treated, the metabolic dysregulation can cause pathophysiologic changes in multiple organ systems, resulting in such medical problems as retinopathy, which

may lead to blindness, end-stage renal disease, and nontraumatic lower extremity amputations; uncontrolled diabetes can also predispose a patient to cardiovascular disease. *Id.* at 13.

### B. Diabetes Treatment

50. The goals when treating patients with type 1 or type 2 diabetes are to: 1) eliminate symptoms related to hyperglycemia (high blood glucose levels); 2) reduce or eliminate long-term complications (i.e., those affecting the eyes, kidneys, nervous system, and circulatory system); and 3) allow the patient a lifestyle as close to normal as possible. Ex. 1109 (Harrison's) at 31. To reach these goals, lowering plasma glucose is a primary aim. *Id.*

51. In 1922, Dr. Fredrick Banting and Charles Best discovered that insulin was secreted by the pancreas. Ex. 1048 (Banting). After isolating insulin, they found that it could be effective in the treatment of diabetes. *Id*. Specifically, insulin is a key mediator of glucose lowering and either administering exogenous insulin or stimulating the body's insulin production will lower blood glucose levels. Thus, beginning in the 1920s, patients diagnosed with diabetes could be treated with insulin injections. For patients with type 1 diabetes, an important goal is designing and implementing an insulin treatment regimen that mimics physiologic insulin secretion. Ex. 1109 (Harrison's) at 34.

52. In 1983, two peptides related to the hormone glucagon were found in the gut, and were named glucagon-like peptide 1 ("GLP-1") and glucagon-like peptide 2 ("GLP-2"). *See generally* Ex. 1049 (Bell). Additional studies discovered that the body naturally synthesizes truncated forms of the GLP-1 peptide, including GLP-1(7-37). *See, e.g.*, Ex. 1051 (Mojsov); Ex. 1050 (Holst 1987). GLP-1(7-37) was found to have an insulinotropic (stimulating insulin secretion) effect while also inhibiting the secretion of glucagon, a hormone that raises blood glucose. Ex. 1051 (Mojsov) at 1-3; Ex. 1050 (Holst 1987) at 4-6. A POSA therefore would have known since the 1980s that GLP-1 and certain of its truncated forms (e.g., GLP-1(7-37)) were potential therapeutic agents for the treatment of diseases such as type 2 diabetes because of their ability to stimulate insulin, inhibit glucagon, and ultimately lower blood glucose levels.

53. As of the priority date of the '122 patent, in addition to traditional lifestyle modifications like improved diet and increased exercise, there were several types of glucose-lowering therapies available to treat type 2 diabetics. The avenues for medical intervention typically fell into two categories: oral and parenteral, though more types of oral treatment were available, and insulin was the primary parenteral. Ex. 1109 (Harrison's) at 36-38, Table 333-12. In the former category, a medical practitioner would most commonly choose from among biguanides, α-glucosidase inhibitors, insulin secretagogues, and thiazolidinediones. *Id*.

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

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

Ex. 1109 (Harrison's) at 36-38, Tables 333-12, -13.

55. In the category of parenteral medications, a medical practitioner would most commonly choose an insulin formulation, to provide greater glucose utilization, *id.* at 37-38, but other injectables, especially those based on GLP-1, were also being developed.

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

56. For almost 100 years before the priority date, it was known that gut hormones are responsible for insulin secretion. *See generally* Ex. 1048 (Banting). And, researchers had long investigated hormones and other peptides derived from the gastrointestinal tract to develop treatments for endocrine disorders such as diabetes. Thus, the use of gut hormones for the treatment of diabetes was long considered a therapeutic option.

57. GLP-1 derivatives (including derivatives of GLP-1(7-37)) were a stronger focus of development in the early and mid-1990s, and these derivatives possessed improved pharmacological properties. *See, e.g.*, Ex. 1046 ('549 patent) at Abstract, 1:9-11, 2:27-32, 3:9-11, 25-30; Ex. 1047 (WO457) at 4:24-29, 5:2-7. The literature repeatedly encouraged the use of these derivatives of GLP-1(7-37) for the treatment of diabetes. Ex. 1046 ('549 patent) at Abstract, 1:9-11, 3:9-11, 55-60; Ex. 1047 (WO457) at Abstract.

**D. Liraglutide Behaves like GLP-1 to Treat Diabetes**

58. Liraglutide was developed as one of the first GLP-1(7-37) analogs or derivatives with protracted effect (i.e., longer half-life). Ex. 1068 (Drucker) at 5; Ex. 1011 (Knudsen 2001) at 3-5; Ex. 1010 (Knudsen 2004) at 2; *see also* Ex. 1069 (Baggio 2004b) at 10 ("Liraglutide, is a fatty-acyl-derivatized, DPP-IV-resistant human GLP-1 analogue. Addition of the fatty acid group enables non-covalent binding to serum albumin, thereby prolonging the circulating half-life and reducing renal clearance. In humans, the half-life of liraglutide is approximately 12 hours, suggesting that a once-daily dosing regimen may be all that is required therapeutically.").

59. Liraglutide was known in the prior art to "reduce[] fasting and postprandial glycemia in diabetic subjects after a single 10 μg/kg subcutaneous injection at 11:00 P.M., in association with inhibition of gastric emptying and

reduced levels of circulating glucagon." Ex. 1068 (Drucker) at 5. It was also understood in the art that liraglutide had been shown, "in a broad spectrum of animal models," "to lower blood glucose and body weight, and to increase or maintain β-cell mass," with each of these effects being "consistent with the known physiological effects of GLP-1." Ex. 1011 (Knudsen 2001) at 6; *see also* Ex. 1030 (Holst 2004) at 4 ("[I]n rats with β-cell deficiencies, NN2211 (now also called Liraglutide) had marked antihyperglycemic effects and greatly delayed development of diabetes.").

60. Knudsen 2001 also reported that, "[i]n humans, a study in type 2 diabetic patients has shown that a single injection of 0.010 mg/kg NN2211 lowered blood glucose from 8.1 ± 1.0 mM to 6.9 ± 1.0 mM (p = 0.004)." Ex. 1011 (Knudsen 2001) at 6; *see also* Ex. 1069 (Baggio 2004b) at 10 ("Once-daily injection of liraglutide for 1 week was associated with improved 24 hour glycaemia and islet α- and β-cell function, as well as reduced 24 hour plasma glucagon and endogenous glucose release in diabetic patients.").

## VIII. SCOPE AND CONTENT OF THE PRIOR ART

61. I identify below the prior art references supporting my expert opinions on unpatentability of claim 15 of the '122 patent, including references rendering the claim obvious. All the references I cite in this document would have been known, and publicly available, to a skilled artisan as of the relevant priority date.

62. The prior art disclosures identified in this expert declaration would have been understood by a skilled artisan in light of the background knowledge that he or she would have had by the applicable priority dates of the '122 patent. Thus, to the extent I list or describe a reference below but do not rely on it as a ground for arguing unpatentability, that prior art should be understood to form part of the background knowledge of a skilled artisan, and to support that person's motivation to combine the prior art with a reasonable expectation of success. Further, to the extent I cite a reference for just one or several of its teachings, I reserve the right to rely on that reference for any other aspect of its teaching.

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

**A. Bridon (Ex. 1014)**

64. U.S. Patent No. 6,514,500 ("Bridon"), titled "Long Lasting Synthetic Glucagon Like Peptide {GLP-1}," issued on February 4, 2003. I understand that Bridon is prior art to the claims of the '122 patent.

65. Ex. 1014 (Bridon) disclosed "modified insulinotropic peptides" ("capable of forming a peptidase stabilized insulinotropic peptide"). According to Bridon, such peptides "are administered to treat humans with diabetes and other related diseases." Ex. 1014 (Bridon) at Abstract. According to Bridon, GLP-1 is an "insulinotropic peptide hormone" that has been implicated as "a possible therapeutic agent for the management of type 2 non-insulin-dependent diabetes mellitus as well as related metabolic disorders, such as obesity." Ex. 1014 (Bridon) at 1:18-22. Bridon noted that although typical insulinotropic peptides like GLP-1, exendin 3, and exendin were useful, their duration of action was known to be quite short, and there was "thus a need to modify GLP-1, exendin 3, exendin 4 and other insulinotropic peptides to provide longer duration of action in vivo, while maintaining their low toxicity and therapeutic advantages." *Id.* at 1:23-40. Bridon noted expressly that its invention "pertains to the therapeutic uses of [modified insulinotropic] compounds, and especially to the use of modified GLP-1(7-36) amide for the treatment of maturity onset diabetes mellitus (type II diabetes)." Ex. 1014 (Bridon) at 1:61-67; *see also id.* at 2:15-28 (same).

66. Bridon described the "insulinotropic activity" of its disclosed compounds as the ability "to stimulate, or cause the stimulation of, the synthesis or expression of the hormone insulin," i.e., what a POSA would have known as a

typical activity of GLP-1 and its analogs and derivatives. *See* Ex. 1014 (Bridon) at 5:16-18. In this regard, Bridon explained:

> The hormonal activity of GLP-1 (7-37) and GLP-1 (7-36) appear to be specific for the pancreatic beta cells where it appears to induce the biosynthesis of insulin. The glucagon-like-peptide hormone of the invention is useful in the study of the pathogenesis of maturity onset diabetes mellitus, a condition characterized by hyperglycemia in which the dynamics of insulin secretion are abnormal. Moreover, the glucagon-like peptide is useful in the therapy and treatment of this disease, and in the therapy and treatment of hyperglycemia.

*Id.* at 5:18-27.

67. Bridon also noted that the modified insulinotropic peptides could be more potent than "normal" GLP-1 because of the extended duration of action of the modified peptides and potentially smaller required dosages:

> The use of an effective amount of modified ITPs [i.e., insulinotropic peptides] as a treatment for diabetes mellitus has the advantage of being more potent than non modified ITPs. Since the modified ITPs are move stable in vivo, smaller amounts of the molecule can be administered for effective tratment. [sic] The present invention is especially suited for the treatment of patients with diabetes, both type I and type II, in that the action of the

> peptide is dependent on the glucose concentration of the blood, and thus the risk of hypoglycemic side effects are greatly reduced over the risks in using current methods of treatment.
>
> The present invention also provides for a method for treating diabetes mellitus in an individual, wherein said method comprises providing an amount of modified ITP sufficient to treat diabetes; where the composition contains a modified ITP.

Ex. 1014 (Bridon) at 18:49-64.

68. In the context of its disclosed invention, Bridon stated that useful peptides would be "'derivatives' of GLP-1 such as GLP-1(7-37) and especially GLP-1(7-36)" and modified versions of each, including those with various amino acid substitutions and modifications. *See, e.g.*, Ex. 1014 (Bridon) at 6:1-64.

**B. Dong (Ex. 1013)**

69. Dong, *Glucagon-Like Peptide-1 Analogs with Significantly Improved in vivo Activity*, in PEPTIDES: THE WAVE OF THE FUTURE (Michal Lebl et al. eds., 2001) ("Dong"), is a chapter appearing in a book published in 2001. I understand that Dong is prior art to the claims of the '122 patent.

70. Dong disclosed that GLP-1 is "a potent and strictly glucose-dependent insulinotropic agent," which "received increasing attention as a possible new

treatment for type 2 diabetes." Ex. 1013 (Dong) at 6. Dong noted, as a POSA would have known, that "[a]lthough [GLP-1's] effectiveness in type 2 diabetes patients has been demonstrated in clinical evaluations, the potential use of the native GLP-1 as a therapeutic agent is greatly hampered by its short plasma half-life. Physiologically, GLP-1 is rapidly degraded by endoproteases." *Id.* Dong therefore reported on "a series of novel human GLP-1 (hGLP-1) analogs" with "greatly improved plasma half-life and significantly enhanced in vivo activity." *Id.*

71. As to activity results, Dong stated that "[t]he *in vivo* studies of this new series of hGLP-1 analogs in normal Sprague-Dawley rats demonstrated that the efficacy of the analogs, in terms of the glucose-dependent stimulation of insulin secretion, is highly correlated with their *in vitro* plasma half-life." Ex. 1013 (Dong) at 7. Dong noted, for example, that analog compound 4, which had a 9.76-hour half-life, showed a 7.6-fold increase in efficacy compared to native GLP-1, "likely due to [the analog's] enhanced enzymatic stability, resulting in an increased circulating half-life." *Id.* In a mouse model, this analog "produced a dose-dependent reduction in blood glucose monitored over a 5-h period." *Id.*

72. Dong summarized:

> In conclusion, we have designed and synthesized a novel class of GLP-1 analogs that have substantially enhanced plasma half-life, while retaining full receptor potency of

> the native hormone. The representative analog, compound 4, is significantly more efficacious than hGLP-1 *in vivo*, and is effective in lowering blood glucose in the [diabetic] mouse model of type 2 diabetes.

Ex. 1013 (Dong) at 7.

**C. Knudsen 2001 (Ex. 1011)**

73. Knudsen, *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26(7) DRUGS OF THE FUTURE 677 (2001) ("Knudsen 2001"), is a review article published in 2001. I understand that Knudsen 2001 is prior art to the claims of the '122 patent.

74. Knudsen 2001 disclosed that GLP-1 has many favorable qualities making it "an obvious drug candidate for the treatment of type 2 diabetes." Ex. 1011 (Knudsen 2001) at 1. Among these, Knudsen 2001 noted GLP-1's ability to "promot[e] glucose-dependent insulin release from the pancreatic β-cells," "lower plasma glucagon in a glucose-dependent manner, decrease the rate of gastric emptying, promote fullness/satiety and stimulate insulin biosynthesis, as well as proliferation of β-cells." *Id*.

75. Knudsen 2001 disclosed, however, that native GLP-1 suffered from a relatively short half-life in the body (e.g., 1-2 hours after subcutaneous administration), and therefore GLP-1-based drugs should use something like "a

protracted formulation of the natural hormone," "analogs or derivatives with improved pharmacokinetic properties." *Id*.

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

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

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

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

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

> In conclusion, the mode of action of GLP-1 seems to be ideal for the treatment of type 2 diabetes, especially obese type 2 diabetes patients. GLP-1 compounds glucose-dependently stimulate insulin secretion and inhibit glucagon secretion, decrease gastric emptying and mediate increased fullness and/or appetite, and directly stimulate growth and rescue of pancreatic β-cells. With this important spectrum of effects of GLP-1, it is conceivable that a GLP-1-based compound could potentially be more effective than any of the current blood glucose lowering drugs available today.

*Id.* at 3.

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

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

83. Knudsen 2001 described NN2211 (liraglutide) as "a full agonist with equal potency to GLP-1 on the cloned human GLP-1 receptor," whose "mechanism of protraction involves binding to albumin, metabolic stability towards DPP-IV and slow release from the injection site." *Id.* at 5.

84. In support, Knudsen 2001 noted that NN2211 had been studied extensively in pigs, where it "lowered blood glucose to near normal levels after 2-4 weeks of once-daily administration and normalized prandial glucose tolerance." *Id.* at 5. Knudsen 2001 also noted that NN2211's efficacy appeared to exceed that of exendin-4, another GLP-1 receptor agonist, and that the "differences between NN2211 and exendin-4 may be explained by the longer half-life of NN2211." *Id.* at 6.

85. Knudsen 2001 concluded:

> In summary, in a broad spectrum of animal models NN2211 has been shown to lower blood glucose and body weight, and to increase or maintain β-cell mass. All the effects are consistent with the known physiological effects of GLP-1. In humans, a study in type 2 diabetic patients has shown that a single injection of 0.010 mg/kg NN2211

> lowered blood glucose from 8.1 ± 1.0 mM to 6.9 ± 1.0 mM ($p = 0.004$). NN2211 is currently in phase 2 clinical trials where it's [sic] long-term efficacy will be evaluated.

*Id.* at 6.

**D. Knudsen 2004 (Ex. 1010)**

86. Knudsen, *Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47 JOURNAL OF MEDICINAL CHEMISTRY 4128 (2004) ("Knudsen 2004"), is a review article published in 2004. I understand that Knudsen 2004 is prior art to the claims of the '122 patent.

87. Knudsen 2004 reported on developments related to the GLP-1 receptor agonist class of compounds, noting "the current belief is that the GLP-1 compound class may be able to control the progression of the type 2 diabetes disease not only by controlling blood glucose but also via several other effects," and appeared to have other broader effects throughout the body, such as protecting from cardiovascular complications. Ex. 1010 (Knudsen 2004) at 1; *see also id.* at 5 (noting that "GLP-1 may even exert a cardiovascular protecting effect either indirectly via lowering of blood glucose and plasma lipids or directly via specific GLP-1 receptors on the heart.").

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

> The only known pharmacological side effect of GLP-1 is nausea and vomiting when administered in high doses. These unwanted effects are mediated by inhibited gastric emptying. However, the vast majority of clinical data indicate that the nausea is transient and that efficient glucose control can be obtained without this side effect. Thus, from a clinical point of view, GLP-1, with its efficacious lowering of blood glucose with little risk of hypoglycemia and its potential for prevention of disease progression, seems ideal for the treatment of type 2 diabetes.

*Id*.

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

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

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

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

> Novo Nordisk has completed phase 2 clinical trials with liraglutide(γ-L-glutamoyl(*N*-α-hexadecanoyl))-$Lys^{26}$,$Arg^{34}$-GLP-1(7-37) (NN2211) (Figure 2) as a once daily injection therapy. Several preclinical and clinical studies have been published. Liraglutide is equipotent to GLP-1 and has a half-life that is more than 10-fold larger that of exendin-4, 8 h vs 26 min after iv administration, respectively. Liraglutide is part of a series of acylated derivatives of GLP-1 that are aimed at being long-acting via two independent mechanisms, self-association and noncovalent binding to plasma albumin fatty acid binding

> sites, resulting in a pharmacokinetic profile with slow absorption and a long half-life. Albumin thus serves as a buffer reservoir for liraglutide. GLP-1 can be acylated at multiple sites with a hexadecanoyl fatty acid and a γ-Glu amino acid as a spacer, and the acylated GLP-1 exhibits retained potency and a long half-life after subcutaneous administration. Also, with a slightly shorter fatty acid, dodecanoyl, it is possible to attach two fatty acids and still have a potent compound with a significantly protracted profile. Spacers other than γ-Glu can be used, e.g., GABA or β-Ala. A potency-destroying SAR has also been generated in which acylation in the N-terminus position 8 leads to a compound about 20 times less potent than GLP-1. Acylation with two fatty acids on both naturally present lysines in positions 26 and 34 destroys potency. Last, simultaneous acylation in position 34 combined with a modification of the natural histidine in position 7 (des-aminohistidine) aimed at making the N-terminus more resistant to DPP-IV also destroys potency. Thus, for acylated derivatives of GLP-1 the SAR is well understood.

*Id.* at 3 (footnotes omitted).

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

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

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

Exenatide (natural exendin-4):

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

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

*Id.*

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

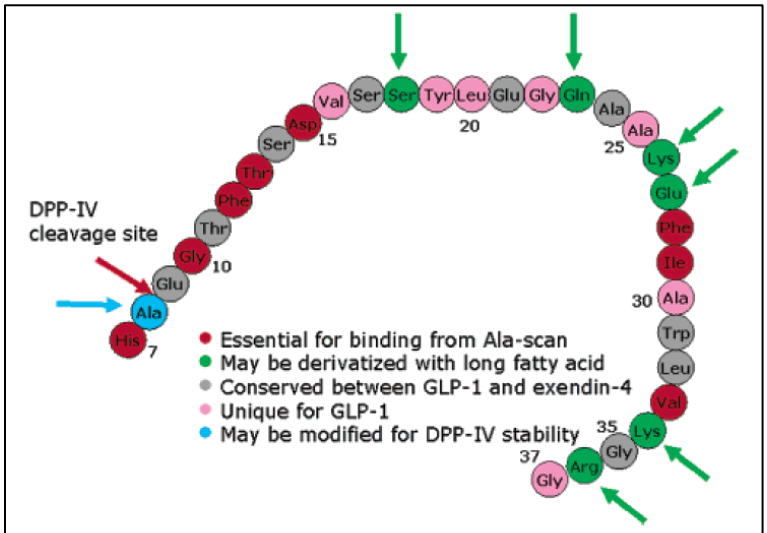



**Figure 3.** SAR figure of GLP-1. All sites essential for binding from Ala-scan are also conserved between GLP-1 and exendin-4. Sites that are possible to modify with fatty acids are only color-coded as such. They are all unique for GLP-1 at the same time.

*Id.*

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

[3] Knudsen 2004 cited to Adelhorst, *Structure-Activity Studies of Glucagon-like Peptide 1*, 269(9) J. BIOLOGICAL CHEMISTRY 6275 (1994), for the alanine-scanning data underlying its summary figure. Ex. 1010 (Knudsen 2004) at 3.

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

97. Regarding treatment of diabetes, Knudsen 2004 disclosed current trial data and summarized that "data indicate that glucose control with the GLP-1 compound class may be significantly better than any of the oral drugs currently on the market for type 2 diabetes." *Id.* at 4-5. Specifically related to liraglutide, Knudsen 2004 disclosed that "[l]iraglutide has been shown to have linear dose-dependent pharmacokinetic properties in man, with a half-life of 11-15 h and a $t_{max}$ of 9-11 h after [subcutaneous] administration and an absolute bioavailability of 55%. Thus, the half-life should be in agreement with full efficacy following once daily administration." *Id.* at 5 (footnotes omitted).

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

### E. Knudsen patent (U.S. Patent No. 6,268,343) (Ex. 1012)

99. U.S. Patent No. 6,268,343 ("Knudsen patent"), titled "Derivatives of GLP-1 Analogs," issued on July 31, 2001. I understand that the Knudsen patent is prior art to the claims of the '122 patent.

100. The Knudsen patent disclosed "GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods for making an[d] using same. The GLP-1 derivatives of the present invention have a protracted profile of action." Ex. 1012(Knudsen patent) at Abstract; *see also id.* at 1:24-27 ("The present invention relates to novel derivatives of human glucagon-like peptide-1 (GLP-1) and fragments and/or analogues thereof which have a protracted profile of action and to methods of making and using them.").

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

102. The Knudsen patent further disclosed that "GLP-1 is the most potent insulinotropic substance known. Unlike [glucose-dependent insulinotropic polypeptide], it is surprisingly effective in stimulating insulin secretion in NIDDM

[i.e., non insulin-dependent diabetes mellitus] patients. In addition, and in contrast to the other insulinotropic hormones (perhaps with the exception of secretin) it also potently inhibits glucagon secretion. Because of these actions it has pronounced blood glucose lowering effects particularly in patients with NIDDM." *Id.* at 2:11-18.

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

104. Knudsen disclosed that, before the priority date of the '122 patent, "[t]he incretin function of GLP-1 … [had] been clearly illustrated," with the "action of the hormone … best described as a potentiation of glucose stimulated insulin release." *Id.* at 2:61-3:11. The Knudsen patent also noted that the beneficial, blood glucose-lowering effects are robust and self-limiting:

> if the plasma GLP-1 concentrations increase either by increased secretion or by exogenous infusion the molar ratio of insulin to glucagon in the blood that reaches the liver via the portal circulation is greatly increased, whereby hepatic glucose production decreases. As a result blood glucose concentrations decrease. Because of the

> glucose dependency of the insulinotropic and glucagonostatic actions, the glucose lowering effect is self-limiting, and the hormone, therefore, does not cause hypoglycaemia regardless of dose. The effects are preserved in patients with diabetes mellitus, in whom infusions off slightly supraphysiological doses of GLP-1 may completely normalise blood glucose values in spite of poor metabolic control and secondary failure to sulphonylurea. The importance of the glucagonostatic effect is illustrated by the finding that GLP-1 also lowers blood glucose in type-1 diabetic patients without residual β-cell secretory capacity.

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

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

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

107. Mechanistically, to achieve these goals, the Knudsen patent disclosed substituting one or both Lys residues in the GLP-1 derivatives with a "lipophilic substituent," *id.* at 12:23-25, although, "[p]referably, the GLP-1 derivatives . . . have only one Lys," *id.* at 12:27-29. *See also id.* at 16:57-65 ("To obtain a satisfactory protracted profile of action of the GLP-1 derivative, one or more lipophilic substituents are attached to a GLP-1 moiety. The lipophilic substituents preferably comprises 4–40 carbon atoms, in particular 8–25 carbon atoms. The lipophilic substituent may be attached to an amino group of the GLP-1 moiety by means of a carboxyl group of the lipophilic substituent which forms an amide bond with an amino group of the amino acid residue to which it is attached."). The Knudsen patent then goes on to identify numerous combinations of amino acid sequences and substituents that it asserts will satisfy these goals and conditions. *See generally id.* at cols. 9-167.

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

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

**F. Additional Prior Art References and Knowledge**

110. I understand that each of the references described below is prior art to the claims of the '122 patent.

*1. Drucker (Ex. 1068)*

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

112. Drucker disclosed that "GLP-1R agonists and DPP-IV inhibitors have shown promising results in clinical trials for the treatment of type 2 diabetes." Ex. 1068 (Drucker) at 1.

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

> NN2211 (liraglutide) is a fatty acid-linked DPP-IV-resistant derivative of GLP-1 designed for subcutaneous administration that exhibits a pharmacokinetic profile compatible with once-daily injection. NN2211 reduced fasting and postprandial glycemia in diabetic subjects after a single 10 μg/kg subcutaneous injection at 11:00 P.M., in association with inhibition of gastric emptying and reduced levels of circulating glucagon. NN2211 has been tested in phase 2 clinical trials.

*Id.* at 5.

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

*2. Gutniak (Ex. 1054)*

115. Gutniak, *Antidiabetogenic Effect of Glucagon-Like Peptide-1 (7-36)Amide in Normal Subjects and Patients with Diabetes Mellitus*, 326 NEW ENG. J. MED. 1316 (1992), was published in 1992, which is earlier than the earliest priority date listed on the face of the '122 patent.

116. Gutniak described the insulinotropic effect of glucagon-like peptides, including GLP-1(7-37). Ex. 1054 (Gutniak) at 1 ("[T]wo shorter forms of GLP-1 — GLP-1 (7-37) and GLP-1 (7-36) amide — exert strong insulinotropic effects in vitro and in vivo."). Gutniak investigated the effects of GLP-1(7-36) amide in normal and diabetic subjects and concluded that it may be useful to treat patients with non-insulin dependent diabetes mellitus. *Id*.

*3. Nauck (Ex. 1056)*

117. Nauck, *Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36 amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients*, 36 DIABETOLOGIA 741 (1993), was published in 1993, which is earlier than the earliest priority date listed on the face of the '122 patent.

118. Nauck described administering GLP-1(7-36) amide to human patients with type 2 diabetes. Ex. 1056 (Nauck) at 1-4. Nauck found that type 2 diabetic patients demonstrated increased insulin levels and a reduction in glucose and glucagon levels after administration of GLP-1(7-36) amide. *Id*. at 3. Nauck concluded that the peptide may be used to normalize fasting plasma glucose concentrations in patients with type 2 diabetes. *Id*. at 3-4.

*4. Orskov (Ex. 1052)*

119. Ørskov, *Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7–36 Amide and Glucagonlike Peptide-1 7–37 in Healthy Subjects are*

*Indistinguishable*, 42 DIABETES 658 (1993), was published in 1993, which is earlier than the earliest priority date listed on the face of the '122 patent.

120. Orskov taught that the GLP-1 polypeptides GLP-1(7-37) and GLP-1(7-36) amide were known to occur in mammals including humans. Ex. 1052 (Orskov) at 1. Orskov also taught that these peptides were known to stimulate insulin secretion and release in humans and inhibit glucagon secretion. Orskov at 658. Summarizing the previous literature, Orskov explained that because of these effects on insulin and glucagon secretion, both GLP-1(7-37) and GLP-1(7-36) amide "have been suggested as a possible treatment for [non-insulin dependent diabetes mellitus]." *Id.* Orskov also studied the biological effects of GLP-1(7-37) and GLP-1(7-36) amide in healthy human subjects and found that both compounds "significantly stimulated insulin and C-peptide [an insulin-related peptide] secretion and significantly decreased plasma glucose and the glucagon concentrations." *Id*. at 2.

*5. U.S. Patent No. 5,512,549 (Ex. 1046)*

121. U.S. Patent No. 5,512,549 (the "'549 patent") is titled "Glucagon-Like Insulinotropic Peptide Analogs, Compositions, and Methods of Use," and it issued on April 30, 1996, which is earlier than the earliest priority date listed on the face of the '122 patent.

122. The '549 patent taught glucagon-like insulinotropic peptide (GLP-1(7-37)) analogs and derivatives. Ex. 1046 ('549 patent) at Abstract. The '549 patent

also taught that other GLP-1 variants and analogs were known in the prior art and were known to stimulate insulin secretion. *See id.* at 2:33-43. The '549 patent described compounds that stimulate insulin production in mammals. *Id*. at 1:9-11, 8:21-25, 9:42-47. The '549 patent also disclosed that the GLP-1(7-37) derivatives may be used in "a method for treating non-insulin dependent diabetes mellitus in a mammal in need of such treatment comprising administering an effective amount of [the GLP-1 derivative]." *Id.* at 3:55-62; *see also id*. at Abstract, 1:9-11, 3:9-11, 9:48-52, 27:4-28:21. The '549 patent further taught that the GLP-1(7-37) derivatives "persist in the serum for longer periods than native GLP-1(7-37) either by showing resistance to DPP IV or by being absorbed and cleared slower than native GLP-1(7-37)." *Id*. at 3:25-30; *see also id*. at 2:27-32.

*6. U.S. Patent No. 6,284,727 (Ex. 1053)*

123. U.S. Patent No. 6,284,727 (the "'727 patent") is titled "Prolonged Delivery of Peptides," and it issued on September 4, 2001, which is earlier than the earliest priority date listed on the face of the '122 patent.

124. The '727 patent taught the specific sequence of GLP-1(7-37) and that it was known to have insulinotropic activity. Ex. 1053 ('727 patent) at 1:25-37. The patent also taught that "certain derivatives [of GLP-1(7-37)] and the use thereof to treat Diabetes mellitus in a mammal" were known. *Id.* at 1:38-42. The '727 patent disclosed that derivatives of GLP-1 polypeptides, including GLP-1(7-37) (including

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

*7. WO 87/06941 (Ex. 1057)*

125. WO 87/06941 ("WO941") is titled "Insulinotropic Hormone," and it was published on November 19, 1987, which is earlier than the earliest priority date listed on the face of the '122 patent.

126. WO941 described the GLP-1 peptide, teaching that "GLP-1 has 37 amino acids in its unprocessed form" and that "unprocessed GLP-1 is naturally converted to a 31 amino acid long peptide (7-37 peptide) having amino acids 7-37 of GLP-1." Ex. 1057 (WO941) at 7. WO941 taught that the 7-37 peptide fragment is an insulinotropic hormone, which is useful for treating diabetes mellitus. *Id.*; *see also id*. at Abstract ("The insulinotropic hormone is useful as a potential therapy for *Diabetes Mellitus*."); 3 (same).

* * *

127. In addition to the references discussed above and throughout this declaration, I utilize the knowledge and expertise of a skilled artisan. 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 that were publicly available prior to the priority date of the '122 patent, regardless of whether they are summarized above, are within the scope of the prior art.

*8. WO 91/11457 (Ex. 1047)*

128. WO 91/11457 ("WO457") is titled "GLP-1 Analogs Useful for Diabetes Treatment," and it was published on August 8, 1991, which is earlier than the earliest priority date listed on the face of the '122 patent.

129. WO457 taught the use of GLP-1 analogs "which have improved characteristics for treatment of diabetes Type II." Ex. 1047 (WO457) at Abstract; *see also id*. ("The analogs may either have an enhanced capacity to stimulate insulin production as compared to glucagon or may exhibit enhanced stability in plasma as compared to GLP-1 (7-37) or both. Either of these properties will enhance the potency of the analog as a therapeutic."). Specifically, WO457 described "analogs of the glucagon-like peptide I fragment 7-36 or 7-37 with improved pharmacological properties." *Id*. at 3:10-14. WO457 disclosed that its invention concerned analogs of truncated forms of GLP-1 like GLP-1(7-37), "which have desirable combinations of characteristics as they relate to potency in potentiating glucose-induced insulin secretion and glucose-induced inhibition of glucagon secretion and to circulating half-life." *Id*. at 4:24-29.

## IX. UNPATENTABILITY OF CLAIM 15 OF THE '122 PATENT

130. As I stated above, I understand that other experts have offered opinions related to the obviousness of the semaglutide peptide, as described for Grounds 1-3. As below, I am offering two opinions related to the '122 patent. First, it is my opinion that a POSA would have been motivated to design a GLP-1 receptor agonist with an extended half-life as compared to the prior art, given the clinical considerations described below. Second, it is my view that the dependent "method of treatment" limitations recited in claim 15 would have been obvious.

131. I understand that other experts are offering the opinion that semaglutide falls within the scope of the GLP-1(7-37) derivatives claimed in claim 1 of the '122 patent and that semaglutide would have been obvious to a POSA in view of the prior art. *See* ¶ 13 above. My opinions are therefore limited to the treatment of diabetes with semaglutide as a GLP-1 derivative that falls within the scope of the claims of the '122 patent. I operate under the assumption that semaglutide, as a GLP-1 derivative claimed in claim 1 of the '122 patent, would have been obvious.

### A. A POSA Would Have Been Motivated to Design a GLP-1 Agonist with an Extended Half-Life

132. As useful as GLP-1 was known to be to treat type 2 diabetes and hyperglycemia, there was a continued desire in the art to provide improved GLP-1 molecules with a protracted mechanism of action, i.e., a longer half-life, regardless

of the route of improvement. Providing an improved GLP-1 molecule like this would be driven by a desire to address several compelling needs.

133. First, it was known in the art that native GLP-1's ability to provide sustained lowering of blood glucose concentration was "only observed with continuous infusion" of the peptide, as demonstrated by studies administering GLP-1 intravenously over a long time course. Ex. 1031 (Holz 2003) at 6-7; Ex. 1055 (Madsbad 2004) at 1 (same). As Holz aptly noted, "this mode of administration is not compatible with general use by the public." Ex. 1031 (Holz 2003) at 7. As a result, this recognition led to efforts to "engineer long lasting analogs of GLP-1 that are synthetic peptides and which exhibit insulinotropic and blood glucose lowering activities in vivo" over a longer time course. Ex. 1031 (Holz 2003) at 7; *see also* Ex. 1083 (Elbrond 2002) at 5-6 (noting that "an increase in exposure from 16 to 24 h of native GLP-1 showed further improvements in glycemic control, indicating the therapeutic importance of full 24-h GLP-1 exposure," and describing liraglutide as an improvement because its extended half-life provided this benefit); Ex. 1108 (Holst 2004b) at 3 (describing liraglutide as an improvement because its "half-life in healthy subjects and patients with T2DM of 10–12 h following a single subcutaneous injection" yielded "adequate 24 h exposure after a single daily injection").

134. Second, a GLP-1 analogue or derivative with a longer half-life could provide a dosing protocol with fewer dramatic fluctuations in drug blood levels and, thus, drug-related side effects, like nausea. *See* Ex. 1108 (Holst 2004b) at 3 (commending liraglutide, with its longer half-life, as an improvement because "large post-injection concentration excursions caused by less long-lived analogues that might be associated with side effects such as nausea are likely to be avoided"); *see also* Ex. 1030 (Holst 2004) at 4 ("in chronic treatment the large postinjection concentration excursions caused by less long-lived analogs, which may be associated with side effects such as nausea, are likely to be avoided"); Ex. 1110 (Giannoukakis) at 3 (in multidose studies of CJC-1131, a GLP-1 receptor antagonist with an extended half-life, only two cases of nausea were reported in the patient population, and the symptom substantially decreased or was eliminated with repeat administration).

135. Finally, providing a GLP-1 receptor agonist with an extended half-life, resulting in less-frequent dosing, would bring "improvements in compliance and convenience" for patients, as patients would strongly prefer once weekly dosing, as compared to the prior art once-daily dosing of liraglutide. *See* Ex. 1083 (Elbrond 2002) at 5 (describing the benefit of liraglutide's longer half-life); *see also* Ex. 1110 (Polonsky) at 2 (identifying roughly 50% of patients as having injection-related

anxiety, which would obviously be alleviated, at least partially, by developing a treatment requiring fewer injections).

### B. Claim 15 of the '122 Patent under Ground 1

136. It is my opinion that claim 15 of the '122 patent would have been obvious under Ground 1.

#### *1. A skilled artisan would have been motivated by Knudsen 2004, the Knudsen patent, Dong, or Bridon to arrive at the invention claimed in claim 15 of the '122 patent*

137. As of the priority date, a skilled artisan would have been motivated by Knudsen 2004**,** the Knudsen patent, Dong, or Bridon to treat hyperglycemia and/or type 2 diabetes in a patient needing such treatment by administering to that patient an effective amount of semaglutide, which is within the scope of claim 1, and rendered obvious by Ground 1.

138. As early as the 1980s, skilled artisans were aware that GLP-1 and related peptides were involved in the mechanism of action of diabetes. Because of this involvement, GLP-1 and its analogs were specifically investigated for use in the treatment of endocrine disorders including diabetes. *See* Section VII.C above.

139. Going further, liraglutide, also known as compound NN2211, had been investigated for use to treat diabetes. *See* Section VII.D above.

140. In short, a skilled artisan would have known that liraglutide was specifically developed as a GLP-1 analog with a longer half-life that could be used

to treat hyperglycemia and/or diabetes. *See* Ex. 1010 (Knudsen 2004) at 3; *see also* Section VII.D above. The same was true for other GLP-1 analogs and derivatives. *See* Ex. 1014 (Bridon) at 8:37-45, 18:49-64 (disclosing the use of more potent GLP-1 derivatives that required smaller doses because of their longer half-lives, used to treat diabetes and other related diseases); Ex. 1013 (Dong) at 7 (disclosing modified GLP-1 molecules with longer half-lives and greater efficacy); Ex. 1012 (Knudsen patent) at Abstract, 1:24-27 (disclosing novel GLP-1 derivatives with a protracted profile of action). In addition, Knudsen 2004 made clear that, by the priority date of the '122 patent, "Novo Nordisk ha[d] completed phase 2 clinical trials with liraglutide … as a once daily injection therapy," including the publication of "[s]everal preclinical and clinical studies." *See* Ex. 1010 (Knudsen 2004) at 3. Knudsen 2004 also made clear that "[l]iraglutide is equipotent to GLP-1" and was "part of a series of acylated derivatives of GLP-1 that are aimed at being long-acting via two independent mechanisms, self-association and noncovalent binding to plasma albumin fatty acid binding sites, resulting in a pharmacokinetic profile with slow absorption and a long half-life." Ex. 1010 (Knudsen 2004) at 3; *see also* Ex. 1014 (Bridon) at 8:37-45, 18:49-64 (disclosing the use of more potent GLP-1 derivatives that required smaller doses because of their longer half-lives, used to treat diabetes and other related diseases); Ex. 1013 (Dong) at 7 (disclosing modified GLP-1 molecules with longer half-lives and greater efficacy, effective in a mouse

model of diabetes); Ex. 1012 (Knudsen patent) at Abstract, 1:24-27, 4:36-5:3 (disclosing novel GLP-1 derivatives with a protracted profile of action, useful to treat such conditions as Type 1 and Type 2 diabetes and obesity).

141. Therefore, as of the priority date, many references, including Knudsen 2004, taught the utility of GLP-1(7-37) and its analogs and derivatives, including liraglutide, to treat hyperglycemia and/or type 2 diabetes. A skilled artisan would therefore have been motivated by at least these teachings to use semaglutide, a GLP-1 analog or derivative falling within the scope of claim 1 of the '122 patent, to treat hyperglycemia and/or diabetes with an effective amount of the semaglutide.

*2. A skilled artisan would have had a reasonable expectation of success of treating hyperglycemia and/or type 2 diabetes in a subject with an effective amount of a GLP-1(7-37) analog, including semaglutide, recited in claim 1*

142. It is my opinion that a skilled artisan would have had a reasonable expectation of success treating hyperglycemia and/or type 2 diabetes by administering to a patient an effective amount of semaglutide, a GLP-1 derivative falling within the scope of claim 1 of the '122 patent. As discussed above, I understand that under Ground 1, semaglutide, a GLP-1 derivative falling within the scope of claim 1 of the '122 patent, would have been obvious. *See* ¶ 13 above. Given that understanding, a skilled artisan would have had a reasonable expectation of

success treating patients with hyperglycemia and/or type 2 diabetes with semaglutide.

143. Claim 15 of the '122 patent claims a "method for treating hyperglycemia and/or type 2 diabetes in a subject, said method comprising administering to a subject in need of such treatment an effective amount of a GLP-1 analog according to claim 1." The prior art, including Knudsen 2004, the Knudsen patent, Dong, and Bridon taught that GLP-1 analogs and derivatives, which includes liraglutide and other GLP-1 analogs, inhibit glucagon secretion and promote insulin secretion and release, encouraging their use as a treatment for hyperglycemia and/or type 2 diabetes. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 1 ("GLP-1 inhibits glucagon secretion"; "GLP-1 … stimulates the natural glucose-induced insulin secretion"; "the current belief is that the GLP-1 compound class may be able to control the progression of the type 2 diabetes disease not only by controlling blood glucose but also via several other effects"); *see also id.* at 3 ("Liraglutide is equipotent to GLP-1"; Figure 3, identifying those sites on GLP-1 that are essential binding and those that may be modified for various functions); Ex. 1014 (Bridon) at 2:42-46, 6:1-22 (GLP and GLP derivatives generally stimulate glucose-dependent insulin secretion and suppress glucagon secretion; the disclosed derivatives are insulinotropic hormones and can affect glucagon level-related activities); Ex. 1013 (Dong) at 6-7 (disclosed GLP-1 analogs cause glucose-dependent stimulation of insulin secretion,

and bind to the GLP-1 receptor, which mediates GLP-1 effects); Ex. 1012 (Knudsen patent) at 8:13-22 (disclosed GLP-1 derivatives "have insulinotropic activity, ability to decrease glucagon, ability to suppress gastric motility, ability to restore glucose competency to beta-cells, and/or ability to suppress appetite/reduce weight").

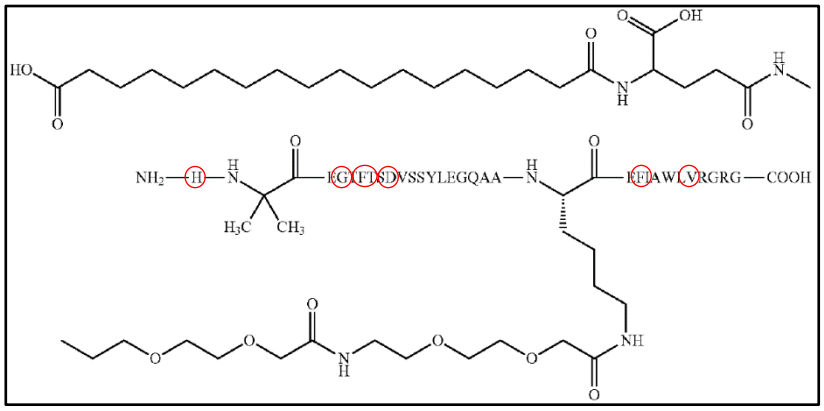
144. As explained above in Section VII.B, insulin is a key mediator for lowering glucose, and glucagon is an anti-insulin hormone that raises glucose, so having GLP-1-like ability to promote insulin secretion and lower glucagon levels identifies a candidate for treatment of hyperglycemia and/or type 2 diabetes. A skilled artisan would therefore reasonably expect that an agent disclosed in the above references, like liraglutide and the other disclosed GLP-1 analogs and derivatives, that can stimulate insulin and/or lower glucagon would be useful to treat diabetes. *See* Sections VII.C-VII.D above.

145. As further support, a POSA would have known from the sequence similarity between liraglutide, the GLP-1 analogs of claim 1, the GLP-1 analogs disclosed in the other prior art described here, and semaglutide (a specific GLP-1 analog falling within the scope of claim 1) that the claimed analog shares all the amino acid residues known to be essential for binding activity of GLP-1. *Compare, for example*, Ex. 1010 (Knudsen 2004), Fig. 3 (conserved residues important for GLP-1 receptor binding, *see* ¶ 94 above) *with* Ex. 1010 (Knudsen 2004), Fig. 1 (liraglutide sequence), Ex. 1012 (Knudsen patent) at 4:52-60 (GLP-1 sequence), Ex.

1013 (Bridon) at 26:49-51 (GLP-1(1-36) sequence to be modified), *and* Ex. 1001 ('122 patent), claim 1 ('122 patent at 123:2-49):[4]

| Knudsen 2004 Fig. 3 essential residue | Present in liraglutide? | Present in '122 patent, claim 1? |
|---|---|---|
| His7 | **Yes** | **Yes**<br>"$Xaa_7$ is L-histidine, D-histidine…" |
| Gly10 | **Yes** | **Yes** |
| Phe12 | **Yes** | **Yes** |
| Thr13 | **Yes** | **Yes** |
| Asp15 | **Yes** | **Yes** |
| Phe28 | **Yes** | **Yes** |
| Ile29 | **Yes** | **Yes** |
| Val33 | **Yes** | **Yes**<br>"$Xaa_{33}$ is Val or Lys" |

146. In addition, I understand that Dr. Flatt identified semaglutide as the compound described in Example 4 of the '122 patent. Reviewing the amino acid sequence of the structure shown in Example 4, below, semaglutide contains the same




[4] These references are exemplary because the amino acid sequences of GLP-1, liraglutide, and other GLP-1 receptor agonists, like exendin 4, were well known in the art. *See, e.g.*, Ex. 1011 (Knudsen 2001) at 680 (sequences of GLP-1 and its derivatives).

amino acids shown in the table above to be an essential residue present in liraglutide (semaglutide residues are circled in red):

147. Finally, to satisfy the requirements of claim 15, a skilled artisan would need only to determine a dose of semaglutide, which falls within the scope of claim 1, to administer to a patient to treat hyperglycemia and/or type 2 diabetes, and the claim requires only that the dose be an "effective dose," i.e., a dose that would be "effective for the treatment of the patient compared with no treatment." It is my opinion that this would have been a routine determination at the priority date for at least two reasons.

148. First, a skilled artisan would have been able to set up a simple and straightforward experiment to determine an effective amount of the semaglutide recited in claim 1. A skilled artisan could have done this by conducting a study in human subjects, but it would have also been possible to use a diabetic animal model.

149. Second, a skilled artisan would have been able to review the "completed phase 2 clinical trials with liraglutide … as a once daily injection therapy" for guidance regarding reasonable starting doses or experimental parameters to be used to determine the effective dose of the semaglutide recited in claim 1.

150. For these reasons, a skilled artisan would have had a reasonable expectation of success treating hyperglycemia and/or type 2 diabetes with an

effective amount of semaglutide, the invention claimed in claim 15 of the '122 patent.

### C. Claim 15 of the '122 Patent under Ground 2

151. It is my opinion that claim 15 of the '122 patent would have been obvious under Ground 2.

152. Like Knudsen 2004 discussed in the previous section, Knudsen 2001 disclosed GLP-1(7-37) analogs and derivatives, including liraglutide. *See, e.g.*, Ex. 1011 (Knudsen 2001) at 5 ("[S]ince compound 5 was equipotent with GLP-1 and had the half-life required to be dosed once daily, compound 5 was selected for clinical development under the name of NN2211 [i.e., liraglutide]"). Knudsen 2001 also taught that liraglutide "was a full agonist with equal potency to GLP-1 on the cloned human GLP-1 receptor." *Id.* Thus, a POSA would have known this disclosed relationship, and from other prior art teachings regarding liraglutide's ability to act like GLP-1, *see* Section VII.D above, that liraglutide stimulated insulin production and decreased glucagon production and would have been useful to treat hyperglycemia and/or type 2 diabetes. *See also* Ex. 1011 (Knudsen 2001) at 5 (in an animal model, liraglutide "increased glucose utilization while at the same time increasing insulin secretion and inhibiting glucagon release, both in a glucose-dependent manner.").

153. Further, Knudsen 2001 taught that liraglutide, like other GLP-1 analogs and derivatives, was designed to, and did, have a longer half-life with high potency, making it suitable for the once-daily treatment of diabetes. *Id.* at 6.

154. As detailed above, and explicitly incorporated herein (*see* Sections IX.B.1, IX.B.2; paragraphs 152-153), the skilled artisan would therefore have been motivated by Knudsen 2001 to treat hyperglycemia and/or type 2 diabetes in a patient needing such treatment by administering to that patient an effective amount of semaglutide, a GLP-1 analog falling within the scope of claim 1. As discussed above, I understand that under Ground 2, semaglutide, a GLP-1 derivative falling within the scope of claim 1 of the '122 patent, would have been obvious. *See* ¶ 13 above. Given that understanding, a skilled artisan would also have had a reasonable expectation of success of treating hyperglycemia and/or type 2 diabetes in that patient by administering to that patient an effective amount of semaglutide, a GLP-1 analog falling within the scope of claim 1 of the '122 patent, as described in Section IX.B.2 above.

**D. Claim 15 of the '122 Patent under Ground 3**

155. It is my opinion that claim 15 of the '122 patent would have been obvious under Ground 3.

156. Bridon, Dong, Knudsen 2001, Knudsen 2004, and the Knudsen patent were discussed in the previous sections, *see* Sections VIII.A–VIII.E above, and each

disclosed derivatives of GLP-1 or a GLP-1(7-37) peptide, including liraglutide (i.e., NN2211). *See, e.g.*, Ex. 1010 (Knudsen 2004) at 2-3; Ex. 1011 (Knudsen 2001) at 5-6; Ex. 1014 (Bridon) at 8:37-45, 18:49-64; Ex. 1013 (Dong) at 6-7; Ex. 1012 (Knudsen patent) at, e.g., Abstract, 1:24-27, 4:18-5:15. Each reference also disclosed that GLP-1 and its derivatives, including liraglutide, as GLP-1-class molecules, stimulated insulin production and inhibited glucagon secretion and would therefore be useful to treat hyperglycemia and/or type 2 diabetes. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 1; Ex. 1011 (Knudsen 2001) at 1-2, 5; Ex. 1014 (Bridon) at 2:42-46, 6:1-22 (GLP and GLP derivatives generally stimulate glucose-dependent insulin secretion and suppress glucagon secretion; the disclosed derivatives are insulinotropic hormones and can affect glucagon level-related activities); Ex. 1013 (Dong) at 6-7 (disclosed GLP-1 analogs cause glucose-dependent stimulation of insulin secretion, and bind to the GLP-1 receptor, which mediates GLP-1 effects); Ex. 1012 (Knudsen patent) at 8:13-22 (disclosed GLP-1 derivatives "have insulinotropic activity, ability to decrease glucagon, ability to suppress gastric motility, ability to restore glucose competency to beta-cells, and/or ability to suppress appetite/reduce weight").

157. Further, the references taught that liraglutide and other similar GLP-1(7-37) analogs and derivatives were designed to have, and had, longer half-lives, indicating that they could sustain diabetes treatment more effectively than GLP-1(7-37) itself. *See, e.g.,* Ex. 1010 (Knudsen 2004) at 3; Ex. 1011 (Knudsen 2001) at 3

("a long dynamic half-life is needed in order to maintain good glucose control on a GLP-1-based drug"), 5-6 (describing liraglutide's longer half-life and ability to lower blood glucose); Ex. 1013 (Dong) at 6-7 (disclosed GLP-1 analogs with longer half-lives were more potent than native GLP-1); Ex. 1014 (Bridon) at 1:10-15 (invention related to modified GLP-1 peptides with long duration of action to treat diabetes and related diseases); Ex. 1012 (Knudsen patent) at 1:24-17 (invention relates to GLP-1 derivatives with protracted profile of action).

158. As detailed above, and explicitly incorporated herein (*see* Sections IX.B.1, IX.C; paragraph 156), a skilled artisan would therefore have been motivated by these teachings to treat hyperglycemia and/or type 2 diabetes in a patient needing such treatment by administering to that patient an effective amount of semaglutide, which is a GLP-1 analog falling within the scope of claim 1. As discussed above, I understand that under Ground 3, semaglutide, a GLP-1 derivative falling within the scope of claim 1 of the '122 patent, would have been obvious. *See* ¶ 13 above. Given that understanding, a skilled artisan would also have had a reasonable expectation of success of treating hyperglycemia and/or type 2 diabetes in that patient by administering to that patient an effective amount of the semaglutide claimed in claim 1 of the '122 patent, as described above. *See* Section IX.B.2, IX.C; paragraph 156.

### E. No Secondary Considerations Overcome *Prima Facie* Obviousness

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

#### *1. No unexpected results*

160. The file history of the '122 patent does not discuss unexpected results, nor does it suggest that treating with semaglutide was somehow "critical." Instead, the evidence described above demonstrates that using semaglutide to treat patients would have been obvious.

#### *2. A POSA would have known there was no long-felt, unmet need for a GLP-1 receptor agonist treatment, nor was there any skepticism in the art*

161. Patent Owner may assert that there was a long-felt but unmet need for the claimed treatment. Such a need did not exist. GLP-1 receptor agonists existed in the prior art before the application for the '122 patent was filed, including agonists based on either GLP-1 or exendin.

162. Moreover, Patent Owner may assert that there was skepticism of the claimed method of treatment with semaglutide. As detailed above, the prior art provided a wealth of knowledge related to expected results from the use of

semaglutide. Thus, any assertions of skepticism would not outweigh the obviousness described above.

## X. RESERVATION OF RIGHTS

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

164. Moreover, during this proceeding I may rely upon documents and/or other materials produced in the proceeding, publicly available documents, and/or any documents the parties have exchanged. Additionally, I may rely on visual aids and/or demonstrative exhibits that I prepare or have prepared on my behalf based upon my opinions.

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

Dated: 3/14/2023

By: John Bantle, MD

Dr. John Bantle

# EXHIBIT A

**EXHIBIT A**

| Exhibit No. | Description |
|---|---|
| 1001 | U.S. Patent No. 8,536,122 |
| 1002 | U.S. Patent No. 8,129,343 |
| 1003 | Prosecution history excerpts for U.S. Patent No. 8,536,122 |
| 1004 | Prosecution history excerpts for U.S. Patent No. 8,129,343 |
| 1010 | Knudsen, *Glucagon-Like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes*, 47(17) J MED CHEM. 4128 (2004) |
| 1011 | Knudsen, *GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development*, 26(7) DRUGS OF THE FUTURE (2001) |
| 1012 | U.S. Patent No. 6,268,343 |
| 1013 | Dong, *Glucagon-Like Peptide-1 Analogs with Significantly Improved in vivo Activity*, *in* PEPTIDES: THE WAVE OF THE FUTURE (Michal Lebl et al. eds., 2001) |
| 1014 | U.S. Patent No. 6,514,500 ("Bridon") |
| 1030 | Holst, *The Incretin Approach for Diabetes Treatment Modulation of Islet Hormone Release by GLP-1 Agonism*, 53 (suppl. 3) DIABETES S197 (2004) |
| 1046 | U.S. Patent No. 5,512,549 |
| 1047 | WO 91/11457 |
| 1048 | Banting, *The Internal Secretion of the Pancreas,* 7 J. LAB. CLINICAL MED. 251 (1922) |
| 1049 | Bell, *Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides*, 302 NATURE 716 (1983) |

| Exhibit No. | Description |
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| 1050 | Holst, *Truncated Glucagon-like Peptide I, an Insulin-Releasing Hormone from the Distal Gut*, 211 (2) FEBS LETTERS 169 (1987) |
| 1051 | 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. CLINICAL INVESTIGATION 616 (1987) |
| 1052 | Ørskov, *Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7–36 Amide and Glucagonlike Peptide-1 7–37 in Healthy Subjects are Indistinguishable*, 42 DIABETES 658 (1993) |
| 1053 | U.S. Patent No. 6,284,727 |
| 1054 | Gutniak, *Antidiabetogenic Effect of Glucagon-Like Peptide-1 (7-36)Amide in Normal Subjects and Patients with Diabetes Mellitus*, 326 NEW ENG. J. MED. 1316 (1992) |
| 1055 | Madsbad, *Improved Glycemic Control with No Weight Increase in Patients with Type 2 Diabetes after Once-Daily Treatment with the Long-Acting Glucagon-Like Peptide 1 Analog Liraglutide (NN2211)*, 27 Diabetes Care 1335 (2004) |
| 1056 | Nauck, *Normalization of Fasting Hyperglycaemia by Exogenous Glucagon-Like Peptide 1 (7-36 amide) in Type 2 (Non-Insulin-Dependent) Diabetic Patients*, 36 DIABETOLOGIA 741 (1993) |
| 1057 | WO 87/06941 |
| 1068 | Drucker, *Enhancing Incretin Action for the Treatment of Type 2 Diabetes*, 26 DIABETES CARE 2929 (2003) |
| 1069 | Baggio, *Glucagon-like Peptide 1 and Glucagon-like Peptide 2*, 18 BEST PRAC. & RSCH. CLINICAL ENDOCRINOLOGY & METABOLISM 531 (2004) ("Baggio 2004b") |
| 1108 | Holst, *Glucagon-Like Peptide 1 and Inhibitors of Dipeptidyl Peptidase IV in the Treatment of Type 2 Diabetes Mellitus*, 4 CURRENT OP. IN PHARM. 589 (2004) ("Holst 2004b") |

| Exhibit No. | Description |
|---|---|
| 1109 | HARRISON'S PRINCIPLES OF INTERNAL MEDICINE Ch. 333 (Eugene Braunwald et al. eds., 15th ed. 2001) |
| 1110 | Giannoukakis, *CJC-1131 ConjuChem*, 4(10) CURRENT OP. IN INVESTIGATIONAL DRUGS 1245 (2003) |
| 1111 | Polonsky, *What's so Tough About Taking Insulin? Addressing the Problem of Psychological Insulin Resistance in Type 2 Diabetes*, 22(3) CLINICAL DIABETES 147 (2004) |