

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

MYLAN PHARMACEUTICALS INC.,

Petitioner,

v.

NOVO NORDISK A/S,

Patent Owner.

Case No. IPR2023-00723

Patent No. 8,129,343

**DECLARATION OF PETER FLATT, PH.D., IN SUPPORT OF PETITION
FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,129,343**

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TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation
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Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)	Bell
U.S. Patent No. 6,514,500	Bridon
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Göke, <i>Glycosylation of the GLP-1 Receptor is a Prerequisite for Regular Receptor Function</i> , 15(4) PEPTIDES 675 (1994)	Göke
Harder, <i>The Effect of Liraglutide, a Long-Acting Glucagon-Like Peptide 1 Derivative, on Glycemic Control, Body Composition, and 24-h Energy Expenditure in Patients with Type 2 Diabetes</i> , 27 DIABETES CARE 1915 (2004)	Harder

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Kenyon, <i>¹³C NMR Studies of the Binding of Medium-Chain Fatty Acids to Human Serum Albumin</i> , 35 J. LIPID RSCH. 458 (1994)	Kenyon
Kim, <i>Development and Characterization of a Glucagon-Like Peptide 1-Albumin Conjugate: The Ability to Activate the Glucagon-Like Peptide 1 Receptor In Vivo</i> , 52(3) DIABETES 751 (2003)	Kim
Knudsen, <i>Potent Derivatives of Glucagon-Like Peptide-1 with Pharmacokinetic Properties Suitable for Once Daily Administration</i> , 43(9) J MED CHEM. 1664 (2000)	Knudsen 2000
Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26(7) DRUGS OF THE FUTURE (2001)	Knudsen 2001
Knudsen, <i>Glucagon-Like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47(17) J MED CHEM. 4128 (2004)	Knudsen 2004

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Larsen, <i>Systemic Administration of the Long-Acting GLP-1 Derivative NN2211 Induces Lasting and Reversible Weight Loss in Both Normal and Obese Rats</i> , 50 DIABETES 2530 (2001)	Larsen
LEHNINGER PRINCIPLES OF BIOCHEMISTRY (David L. Nelson et al. eds., 4th ed. 2005)	Lehninger
Luna, <i>Oral Agents in the Management of Type 2 Diabetes Mellitus</i> , 63 AM. FAM PHYSICIAN 1747 (2001)	Luna
MacDonald, <i>The Multiple Actions of GLP-1 on the Process of Glucose-Stimulated Insulin Secretion</i> , 51 (suppl. 3) DIABETES S434 (2002)	MacDonald
Madsbad, <i>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)</i> , 27 DIABETES CARE 1335 (2004)	Madsbad
Markussen, <i>Soluble, Fatty Acid Acylated Insulins Bind to Albumin and Show Protracted Action in Pigs</i> , 39(3) DIABETOLOGIA 281 (1996)	Markussen
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Pyne, <i>Cyclic Nucleotide Phosphodiesterases in Pancreatic Islets</i> , 46 DIABETOLOGIA 1179 (2003)	Pyne
Rando, <i>Functional Incorporation of Synthetic Glycolipids into Cells</i> , 77(5) PROC. NATL. ACAD. SCI. USA 2510 (1980)	Rando
Ribel, <i>NN2211: A Long-Acting Glucagon-Like Peptide-1 Derivative with Anti-Diabetic Effects in Glucose-Intolerant Pigs</i> , 451 EUR. J. PHARMACOLOGY 217 (2002)	Ribel
WO 03/074005	Sato
Sewald, PEPTIDES: CHEMISTRY AND BIOLOGY (2002)	Sewald
Victoza prescribing information (June 2022)	Victoza label

I. INTRODUCTION

1. My name is Peter R. Flatt, Ph.D. I have been retained by Mylan Pharmaceuticals Inc. (“Mylan”). I understand that Mylan intends to petition for inter partes review (“IPR”) of U.S. Patent No. 8,129,343 (“the ’343 patent”), Ex. 1002, which is assigned to Novo Nordisk A/S (“Patent Owner”). As part of the petition, I understand Mylan will request that the United States Patent and Trademark Office (“USPTO”) cancel claims 1-6 of the ’343 patent (“the challenged claims”) as unpatentable. I submit this expert declaration to address and support Mylan’s IPR petition for the challenged claims of the ’343 patent.

II. QUALIFICATIONS AND BACKGROUND

A. Education and Experience; Prior Testimony

2. I am currently a Professor of Biomedical Science, Director of the Biomedical Sciences Research Institute, and Head of Diabetes Research Group at Ulster University at Coleraine, Northern Ireland.

3. I received a Bachelor of Science Degree in Biology and Chemistry from Aston University in 1974. In 1977, I received a Ph.D. from Aston University where my research was primarily related to insulin and glucagon, including studies on obesity and diabetes. In 2018, I received a Doctor of Sciences from Ulster University for pioneering research on gut hormones and peptide therapeutics for diabetes.

4. In 1978, after obtaining my Ph.D., I joined the University of Uppsala as a Postdoctoral Research Fellow in the Department of Medical Cell Biology.

5. In 1980, I joined the University of Surrey where I was a lecturer and senior lecturer in the Department of Biochemistry.

6. In 1989, I joined Ulster University as a Professor of Biomedical Sciences and Head of Diabetes Research Group in the School of Biomedical Sciences. In 1992, I became the Director of the Biomedical Sciences Research Centre. In 1994, I became the Head of the School of Biomedical Sciences. In 2012, I became Course Director of BSc (Honours) Biomedical Science Degree Courses. In 2017, I became the Director of Biomedical Sciences Research Institute, which houses approximately 150 principal investigators and was rated in the top five UK Units for research power in biomedical sciences in the nationwide REF assessment in 2021.

7. Throughout my career, my research has focused on peptides for use in the treatment of diabetes and/or obesity, including naturally occurring peptides and analogues of naturally occurring peptides. Specifically, my research has focused on experimental diabetes research on gut hormones, peptide therapeutics, drug discovery, cell therapy, beta-cell stimulus-secretion coupling and islet cell function.

8. I have published numerous books, articles, abstracts, and the like, related to experimental diabetes research on gut hormones, peptide therapeutics,

drug discovery, cell therapy, beta-cell stimulus-secretion coupling and islet cell function, including:

- a. Four multi-author edited international research texts.
- b. Six edited proceedings (i.e., colloquia, conferences, seminars, etc.).
- c. 110 reviews and book chapters.
- d. 570 original peer-reviewed scientific papers.
- e. 29 patented inventions.

9. My publications have been cited more than 25,200 times and I have an h-index of 75. I have presented approximately 100 research lectures at national or international conferences in more than 20 countries around the world.

10. I have received numerous awards throughout my career for my work in the field of diabetes research, including:

- a. Elected Fellow of the Institute of Biology (FIBiol now FBS)
- b. Elected Fellow of the Royal Society of Chemistry (FRSC)
- c. Recipient of Mary Jane Kugal Award of Juvenile Diabetes Federation International
- d. Recipient of Biochemistry Medal of Irish Section of the Biochemical Society
- e. Elected Member of the Royal Irish Academy (MRIA) – Ireland's premier Learned Body for Sciences and Humanities

- f. Awarded Ulster University Senior Distinguished Research Fellowship
 - g. Dorothy Hodgkin Award Lecturer of Diabetes UK
 - h. Niall O'Meara Lecturer of Irish Endocrine Society
 - i. Ernst-Friedrich Pfeiffer Memorial Lecture, European Association for the Study of Diabetes (AIDPIT)
 - j. Steno Rounds Medal, Steno Diabetes Centre, Denmark
 - k. Elected Fellow of Higher Education Academy (FHEA)
 - l. Listed in ExpertsGate Objective Rankings of Medical Expertise 2022 as No 2 Worldwide Expert for Experimental Diabetes and No 3 for Insulin Secretion
11. In the previous four years, I have provided testimony in the following proceedings:

Finland

- Sitagliptin and metformin (Janumet, Revocation MSD's SPC)

- Court appearance: Merck & Co., Inc v. Teva Pharmaceuticals

Sweden

- Sitagliptin and metformin (Janumet Revocation MSD's SPC)

- Court appearance: MSD v KRKA d.d. Novo mesto

Portugal

- Sitagliptin and metformin (Janumet Revocation MSD's SPC)

- MSD v Pharmakern (2022)

- MSD v Sandoz (2022)
- MSD v Stada Arzneimittel AG and Ciclum Farma Unipessoal Lda (2023)

12. My qualifications and publications are further described on my *curriculum vitae*, which can be found at Exhibit 1021.

B. Legal Standards and Materials Reviewed

13. In preparing and forming my opinions set forth in this declaration, I have been informed of the relevant legal principles. I have applied my understanding of those principles in forming my opinions. My understanding of those principles is summarized below.¹

14. I have been informed that Mylan bears the burden of proving unpatentability by a preponderance of the evidence. Counsel has informed me that this “preponderance of the evidence” standard means Mylan must show that

¹ In performing my analysis and reaching my opinions and conclusions, I have been informed of and been advised to apply various legal principles relating to unpatentability, which I set forth herein. In setting forth these legal standards, it is not my intention to testify about the law. I only provide my understanding of the law, as explained to me by counsel, as a context for the opinions and conclusions I am providing in this declaration.

unpatentability is more probable than not. I have taken these principles into account when forming my opinions.

15. I understand that my opinions regarding unpatentability are from the viewpoint of a person having ordinary skill in the art (“POSA”), i.e. in the field of technology of the patent as of the priority date of the ’343 patent. I have also been informed that claims should be given their plain and ordinary meaning in light of the intrinsic evidence (i.e., the specification and the prosecution history) from the perspective of a POSA.

16. I also understand 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.

17. I was informed that claims of a patent may be found obvious if, in view of the prior art, a POSA would have been motivated to combine the teachings of the prior art to arrive at the claimed subject matter with a reasonable expectation of success in doing so. I further understand that absolute predictability of success is not required for patent claims to be found obvious.

18. 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 POSA has good reason to pursue the known options within their

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.

19. I was also informed that the claims of a patent may be found obvious if, in view of the prior art, the claimed subject matter involves combinations of known elements that would have been obvious to try.

20. I also understand from counsel that claims of a patent directed to chemical compounds may, in some instances, require what's referred to as a lead compound obviousness analysis. I was informed that when applicable this lead compound analysis involves a two-part test. First, Mylan must show that a POSA would have selected a prior art compound, or compounds, as a "lead compound" (i.e., a compound that would be a natural choice for further development efforts). I understand a POSA could identify multiple compounds as "lead compounds" so long as a POSA would have had a reason to select each proposed lead compound.

21. Second, Mylan must show that a POSA would have been motivated to modify the lead compound(s) to arrive at the claimed compound. I understand the motivation to modify a lead compound can come from any number of sources and does not need to be explicitly disclosed in the prior art.

22. A list of the materials I considered, in addition to my experience, education, and training, in providing the opinions contained herein is attached as Appendix A.

C. Scope of Work

23. I have been retained by Mylan as a technical expert to provide various opinions regarding the '343 patent. I am being compensated for my work in this case at a rate of £500 (GBP) per hour plus expenses. My compensation is in no way tied to the outcome of this case or to the content of this declaration. I do not have any current or past affiliation with Patent Owner, any affiliates of Patent Owner presently known to me, or the named inventors of the '343 patent.

III. PERSON OF ORDINARY SKILL IN THE ART

24. I understand my analysis is to be conducted from the perspective of a POSA as of the priority date of the '343 patent. I have also been informed by counsel that in defining a POSA, the following factors may be considered: (1) the educational level of the inventors; (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).

25. A POSA would have understood the prior art references cited herein and would have the capability to draw inferences from them. It is understood that, to the extent necessary, a POSA may collaborate with one or more other POSAs and/or others with relevant knowledge for one or more aspects with which the others may have expertise, experience, and/or knowledge. Additionally, a POSA could have had a lower level of formal education than described in the following definitions if the person has a higher degree of experience.

26. In my opinion, the following definition of a POSA applies to the claims of the '343 patent. The subject matter of the claims of the '343 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 glucagon-like peptide 1 ("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, pharmaceuticals, pharmaceutical sciences, chemical engineering, biochemical engineering or related fields, with at least two years of experience in 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.

27. Alternatively, the POSA (1) would be a highly skilled scientist lacking an M.D., Pharm.D., or doctoral degree, but (2) (a) would have more than five years of experience in the area of developing therapeutic proteins or peptides and/or (b) would have 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.

28. 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.

29. With respect to claims 2 and 5 of the '343 patent, the team would have included an individual with a Ph.D. in chemistry, biochemistry, pharmaceuticals, pharmaceutical sciences, chemical engineering, biochemical engineering, or related fields, with at least two years of experience in the formulation of therapeutic peptides or proteins.

30. With respect to the subject matter of claim 3 and 6 of the '343 patent, the team would have included an individual with an M.D. and experience treating patients having type-2 diabetes or related conditions.

31. As explained above, and as is evident from my CV, I met the qualifications of a POSA as of the priority date of the '343 patent. Within this definition, my background focuses on the chemical, biological, and biochemical aspects of the claims of the '343 patent. This includes aspects of the claims related to the chemical structures of the claimed peptides, their biological and biochemical effects, and related issues.

IV. THE '343 PATENT

32. I have read the '343 patent, including its claims, which is titled "Acylated GLP-1 Compounds."

33. I understand that the '343 patent has 6 issued claims, each of which is written in independent form.

34. The '343 patent lists Jesper Lau, Paw Bloch, and Thomas Kruse Hansen as inventors.

35. The '343 patent was filed on March 20, 2006, as U.S. Patent Application No. 11/908,834, which was a national-stage entry of PCT/EP2006/060855. The '343 patent claims priority to U.S. Provisional Application No. 60/664,497, filed on March 23, 2005, as well as European application No. 05102171, filed March 18, 2005.

36. I understand the earliest priority date to which the challenged claims of the '343 patent are entitled is March 18, 2005, the filing date of European application

37. The '343 patent has six independent claims. The first claim (as subsequently corrected) recites:

[illegible]

38. The '343 patent describes "SEQ ID No:7" as follows:

MPI EXHIBIT 1020 PAGE 21

Ex. 1002 ('343 patent) at 103.

39. Claim 2 is an independent claim that recites a “pharmaceutical composition” that includes the same compound recited in claim 1 (depicted again in full) and “a pharmaceutically acceptable excipient.”

40. Claim 3 is an independent claim that recites a “method for treating type 2 diabetes in a subject” by administering “an effective amount” of a composition comprising the same compound depicted in claim 1 and an excipient.

41. Claim 4, like claim 1, is directed to a compound, but this time is specified by its chemical name: N- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

42. Claim 5, like claim 2, recites a “pharmaceutical composition” that includes the same compound recited in claim 4 (recited again in full by name) and “a pharmaceutically acceptable excipient.”

43. Claim 6, like claim 3, recites a “method for treating type 2 diabetes in a subject” by administering “an effective amount” of a composition comprising the same compound recited in claim 4 and an excipient.

44. The only apparent difference between the compounds of claims 1-3 and 4-6 is that claims 4-6 specify the stereochemistry of the glutamic acid spacer attached

at Lys²⁶: “N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(**S**)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg 34]GLP-1-(7-37)peptide.” Ex. 1002, claims 4-6 (emphasis added).

V. CLAIM CONSTRUCTION

45. I have been informed that claim terms should be given their plain and ordinary meaning in light of the intrinsic evidence (i.e., the specification and the prosecution history) from the perspective of a POSA. I also understand that while extrinsic evidence (e.g., scientific publications) may be considered when interpreting the meaning of claim terms in some circumstances, it is generally given less weight than intrinsic evidence.

46. There are no terms relevant to my opinions that require construction beyond the plain and ordinary meaning.

VI. SUMMARY OF OPINIONS

47. In my opinion, the challenged claims of the '343 patent would have been obvious over the combinations of prior art references set forth below, optionally and further in view of the knowledge of a POSA and the state of the art as of the priority date of the '343 patent.

48. As explained above, the challenged claims recite semaglutide (and claims 1-3 also include its stereoisomers)², compositions containing semaglutide, and methods of treating type-2 diabetes using semaglutide compositions. *Supra* Section IV; *infra* Section VII.C.5. In my opinion, semaglutide would have been obvious in view of the prior art.

49. Well before the priority date of the '343 patent, other GLP-1(7-37) analogues had been identified and developed as therapeutic agents. *Id.* In my opinion, a POSA would have identified at least one specific prior art GLP-1(7-37) analogue, liraglutide, as worthy of further development. Specifically, liraglutide, Novo Nordisk's first-generation GLP-1(7-37) analogue, would have been an obvious starting point for a POSA motivated to develop long-lasting GLP-1(7-37) analogues. *See, e.g.*, Ex. 1012 (Knudsen Patent) at 187:40-188:4, 191:32-192:67.

50. Liraglutide exhibited many promising properties and had been successful in phase II clinical trials before the priority date of the '343 patent. *See, e.g.*, Ex. 1034 (Knudsen 2000) at 2; Ex. 1011 (Knudsen 2001) at 5-6; Ex. 1010

² It appears claims 1-3 and 4-6 differ only because claims 4-6 specify the stereochemistry of the glutamyl spacer attached at Lys²⁶. Therefore, claims 1-3 theoretically cover not only semaglutide, which contains the (S)-isomer, but also the (R)-isomer of the glutamyl compound.

(Knudsen 2004) at 5; Ex. 1031 (Holz) at 7; Ex. 1073 (Joy) at Abstract; Ex. 1055 (Madsbad) at 1. However, even though it showed promising properties, a POSA would not have stopped at liraglutide, and would have continued to investigate other GLP-1(7-37) analogues with long half-lives and suitable therapeutic properties. For example, a POSA would have understood that while liraglutide appeared suitable as a once-daily treatment option, a GLP-1 analogue with an even longer duration of action would be beneficial for patients. Accordingly, in my opinion, a POSA would have been motivated to modify liraglutide to obtain a GLP-1(7-37) analogue with a longer half-life and suitable therapeutic properties. Further, as explained in detail below, a POSA would have been motivated to introduce the specific chemical modifications needed to arrive at semaglutide and would have had a reasonable expectation of success in doing so in view of the teachings of the prior art. *Infra* Sections VIII.B-D.

51. In addition, counsel has informed me that a “lead compound” obviousness analysis may not be required for the challenged claims to be found unpatentable as obvious. If that is the case, it is my opinion that a POSA would have been motivated to make semaglutide based on the GLP-1 analogues disclosed in the prior art, for example, liraglutide, and would have had a reasonable expectation of success, or considered it obvious to try. First, as explained above, a POSA would have been motivated to make GLP-1(7-37) analogues generally in view of their

promising therapeutic properties. Second, the individual chemical moieties and modifications that resulted in semaglutide (i.e., the amino acid substitutions, a di-AEEA spacer, a glutamic acid linker, and a fatty diacid) were known in the art. Third, using standard drug development research practices and laboratory techniques, a POSA would have naturally arrived at semaglutide.

52. Accordingly, for the reasons set forth above, it is my opinion that the challenged claims are unpatentable as obvious.

VII. BACKGROUND ON DIABETES, THE TREATMENT OF DIABETES, AND GLP-1 ANALOGUES

A. Diabetes

53. Diabetes is defined generally as a group of disorders in which insulin is either not produced (i.e., type 1) or is not normally processed and secreted by the body (i.e., type 2). *See, e.g.*, Ex. 1074 (Korc) at 2-4; Ex. 1099 (PDR) at 7. Normally, the body can release or modulate the amount of insulin present in the bloodstream depending on blood glucose levels. *See, e.g.*, Ex. 1074 (Korc) at 2-4. Insulin, a peptide hormone produced by beta cells in the pancreas, serves to control glucose levels in the bloodstream. *Id.* at 1. As a result, diabetic individuals can suffer from high blood glucose levels (i.e., hyperglycemia) and debilitating complications, if left unchecked and untreated. *See generally id.*

B. The Treatment of Diabetes

54. As of the priority date of the '343 patent, a POSA would have understood that several treatment options were approved, or were being developed, for the treatment of diabetes. In general, these treatments were aimed at lowering blood glucose levels. Indeed, it was over 120 years ago when Bayliss and Starling discovered that peptides, such as secretin (a peptide secreted by the gut), can regulate physiological processes. *See generally* Ex. 1078 (Bayliss). Since then, researchers have isolated, characterized, and studied many other peptide hormones from the pancreas and gastrointestinal tract, and have investigated numerous potential therapies for the treatment of diabetes. Below I briefly summarize various classes of diabetes drugs and their status as of the priority date.

1. Insulin

55. Banting and Best first isolated insulin in 1921, and shortly thereafter it was available commercially to patients as a diabetes treatment. *See, e.g.*, Ex. 1048 (Banting) at 14-15. However, because insulin suffers from a short half-life, constant monitoring of blood glucose levels and repeated insulin injections are required to effectively manage diabetes. Ex. 1077 (Takiya) at 10-11.

56. While insulin has remained a common treatment, POSAs continue to be motivated to improve and optimize a number of treatment options. For example, extended-action insulin formulations have been developed and marketed, and insulin

remains a common treatment to this day even for poorly controlled type-2 diabetes.

Id. Even with an acceptable treatment option like insulin on the market, researchers continued to investigate and develop other options to manage the disease, particularly type-2 diabetes.

2. Biguanides

57. Another long-used diabetes treatment agent is the guanidine, or biguanidine, class of compounds. *See, e.g.,* Ex. 1070 (Luna) at 6. Guanidine is a naturally occurring small molecule compound that was isolated and first used to treat diabetes in the 1920s. Like insulin, researchers continued to investigate this class of compounds and developed treatment options based on the biguanides. *Id.* Despite concern about adverse effects of certain members of this class, this work ultimately led to metformin being approved in the United States in the 1990s, a treatment still popular today. *Id.; see also* Ex. 1082 (Edwards) at 1. Metformin reduces blood glucose levels through several mechanisms of action, primarily by inhibiting hepatic glucose production and alleviating insulin resistance. *See, e.g.,* Ex. 1070 (Luna) at 6; Ex. 1082 (Edwards) at 1. While metformin is generally considered a useful diabetes treatment option, it can cause undesirable side effects and often fails to control blood glucose adequately. *See, e.g.,* Ex. 1070 (Luna) at 6; Ex. 1082 (Edwards) at 1.

3. Sulfonylureas

58. Sulfonylureas have also been used and investigated for their potential to treat diabetes going back to at least the 1950s. *Id.* at 2, 5. Several sulfonylurea drugs had been developed and marketed well before the priority date of the '343 patent (e.g., glipizide, glyburide, glimepiride). *Id.* at 3. While this class of compounds is generally effective and useful for the treatment of diabetes by stimulating insulin secretion, it can cause hypoglycemia and weight gain, both of which are significant concerns. *Id.* at 2, 5. Also, patients often fail to manage their diabetes adequately in the longer-term using sulfonylureas as a first in line treatment. *Id.* at 5.

4. Thiazolidinediones

59. In the mid-1990s, thiazolidinediones ("TZDs") were approved to treat diabetes in the United States. *See, e.g.*, Ex. 1077 (Takiya) at 4-5; Ex. 1070 (Luna) at 7-8. These small molecule compounds showed promise initially, but it was later discovered that they can cause hepatic failure resulting in patient death, which caused the FDA to remove troglitazone (an early TZD drug) from the market. *See, e.g.*, Ex. 1077 (Takiya) at 4-5; Ex. 1070 (Luna) at 7-8. Other TZD agents that remain on the market today are linked to significant side effects, like fluid retention, weight gain, and may also be linked to cardiovascular issues and bladder cancer. *See, e.g.*, Ex. 1077 (Takiya) at 4-5; Ex. 1070 (Luna) at 7-8.

5. α -Glucosidase Inhibitors and Meglitinides

60. Other agents approved in the 1990s, like α -glucosidase inhibitors and meglitinides, which are related to sulfonylureas, are used modestly at best because of their impractical durations of action, need for multiple doses each day, relative ineffectiveness, or undesirable side effects. *See, e.g.*, Ex. 1077 (Takiya) at 8-9; Ex. 1070 (Luna) at 8.

6. DPP-4 and PDE3 Inhibitors

61. Likewise, before the priority date of the '343 patent, beginning in the 1990s, dipeptidyl peptidase-4 ("DPP-4") inhibitors, small-molecule compounds designed to inhibit the DPP-4 enzyme known to degrade incretin peptides (e.g., glucagon-like peptide-1), were also being investigated. *See generally, e.g.*, Ex. 1100 (Holst 2003). Because of the close relationship between DPP-4 inhibitors and GLP-1, the two were often researched in tandem. *See generally, e.g.*, Ex. 1100 (Holst 2003). However, because DPP-4 inhibitors indiscriminately shut down metabolism of a vast array of different peptide substrates (i.e., not just limited to incretin peptides that produced antidiabetic effects), there was skepticism in the scientific community about the specificity and safety of these agents.

62. Similarly, attempts were made around the same time to develop a drug that could selectively inhibit phosphodiesterase 3 ("PDE3"), an enzyme known to limit insulin secretion by promoting the cellular breakdown of cyclic AMP. *See*

generally, e.g., Ex. 1076 (Pyne). However, like DPP-4 inhibitors, there were concerns that indiscriminately inhibiting all PDE3 activity (or even other phosphodiesterase enzymatic activity) could have significant safety implications and may not be effective.

7. The Rise of GLP-1 Based Drugs

63. As explained above, many diabetes treatment options were approved or were being investigated by the priority date of the '343 patent. However, many of these classes of drugs had waning interest from the scientific community given their side effects and because other options began to emerge in the 1990s and early 2000s.

64. For example, insulin formulations, including extended action insulin formulations, were available as of the priority date. Additionally, as of the priority date, second and third generation sulfonylureas were being marketed and POSAs did not see room for improvement. As another example, metformin, while one of the most highly prescribed medications in the world, had been used since the mid-1990s and POSAs were seeking improved treatments. Others, like TZDs, α -glucosidase inhibitors, and meglitinides were unattractive because of serious side effects, their relative ineffectiveness, or because of their short duration of action.

65. Thankfully, new classes of potential diabetes treatment agents began to emerge in the 1990s and early 2000s. In particular, by the priority date of the '343

patent, drugs aimed at taking advantage of the insulinotropic effect of GLP-1³ had been synthesized, studied, and were being advanced in clinical trials. And while it had long been known that peptide hormones from the gastrointestinal tract are responsible for a so-called insulinotropic effect (i.e., the stimulation of insulin secretion from the pancreas), scientists were not able to isolate and characterize them in detail until later technological advancements were developed.

66. In fact, it was in the 1980s that Bell discovered the peptide derived from the proglucagon gene in the gut that was responsible for an insulin-releasing effect, which was named GLP-1. *See generally* Ex. 1049 (Bell). Additional studies conducted in the 1980s showed that GLP-1(7-37) was truncated at the N-terminus before secretion and served as a natural incretin. *See generally, e.g.*, Ex. 1051 (Mojsov). These truncated forms of GLP-1, including GLP-1(7-37), were found to exhibit particularly powerful insulinotropic effects while also inhibiting the secretion of glucagon. *See, e.g.*, Ex. 1051 (Mojsov) at 2. Thus, beginning in the 1980s, researchers were well aware of GLP-1 and its truncated forms and their potential as therapeutic agents for the treatment of diseases such as type-2 diabetes.

³ GLP-1 is a hormone produced by the intestine that lowers blood-glucose levels by stimulating insulin production and secretion in the pancreas. *See, e.g.*, Ex. 1017 (Drucker 2001) at 1; Ex. 1100 (Holst 2003) at 31.

67. What's more, scientists were aware of another incretin peptide secreted by the gut that shared an ability with GLP-1 to induce an insulintropic effect. Glucose-dependent insulintropic peptide ("GIP"), a 42 amino acid peptide that is secreted from intestinal K-cells, was recognized as a glucose-dependent stimulator of insulin secretion. Ex. 1084 (Gault) at 1. Further, it was determined that GIP had an *in vitro* half-life of about 3-5 minutes. *Id.* Because of these properties, researchers began investigating GIP as a potential antidiabetic agent. In particular, various analogues of GIP with amino acid substitutions (to convey DPP-4 resistance) or acylation of fatty acids (to increase half-life) were investigated with the hope of producing a peptide that retained the important antidiabetic properties but with a longer half-life. *See generally, id.* However, the development of GIP analogues was still in early stages and the picture surrounding these agents, while promising, remained cloudy. *See, e.g., id.* at 1-2.

68. There was also an interest in peptides based on the naturally occurring peptide exendin. Exendin, a 39 amino acid peptide with approximately 50% sequence similarity to GLP-1, is derived from the Gila monster, a venomous lizard native to the southwestern United States. *See, e.g.,* Ex. 1031 (Holz) at 9. It was discovered that exendin is a DPP-4 resistant agonist at the mammalian GLP-1 receptor, meaning that it "activates" the receptor to produce its insulintropic activity. *Id.* This DPP-4 resistance was conveyed by glycine (Gly) instead of an

alanine (Ala) at the equivalent N-terminal amino acid position 8 in GLP-1. *See, e.g., id.* While one such exendin-based peptide, exenatide (Byetta), eventually made it to market, there were concerns that a non-human-based peptide could generate antibodies and cause serious adverse effects. *See, e.g.,* Ex. 1010 (Knudsen 2004) at 2-3. A POSA would have recognized that while these exendin analogues should be investigated, it would be preferential to design a drug based on a human peptide, which would be less likely to cause adverse reactions and side effects.

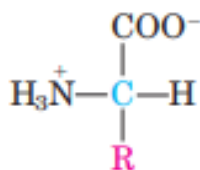
69. However, as noted above, GLP-1-based agents, another class of diabetes treatment options, began to emerge from the rest in the 1990s. Indeed, by the priority date of the '343 patent, the GLP-1 class of peptides had emerged as one of the most, if not *the* most, promising class of diabetes drugs. And by the priority date of the '343 patent, GLP-1 analogues, including liraglutide (also known as NN2211), had been synthesized, studied, and were being advanced in clinical trials. *See generally, e.g.,* Ex. 1010 (Knudsen 2004); Ex. 1031 (Holz); Ex. 1080 (Chang); Ex. 1081 (Degn); Ex. 1082 (Edwards); Ex. 1083 (Elbrond); Ex. 1085 (Harder); Ex. 1108 (Holst 2004b); Ex. 1090 (MacDonald); Ex. 1087 (Ribel). In the words of Lotte Knudsen, who was instrumental in developing liraglutide for Novo Nordisk, it was “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.” Ex. 1010 (Knudsen 2004) at 3.

70. The GLP-1 analogues were also shown in the prior art to demonstrate the potential for meaningful weight loss in over-weight patients, making it an even more attractive candidate for further development. Indeed, Larsen reported that “long-acting GLP-1 derivatives may prove efficient as weight-reducing therapeutic agents for over-weight patients with type-2 diabetes.” Ex. 1086 (Larsen) at 1.

C. Peptides and GLP-1 Analogues

1. General Peptide Chemistry

71. GLP-1 analogues can be broadly categorized as peptides. Peptides are made of amino acids, or amino acid “residues,” and each amino acid is covalently bound to a neighboring amino acid to produce a polymeric chain. Ex. 1036 (Lehninger) at 26. All amino acids share a common core chemical structure:



Id. at 17. Amino acids differ from one another by their side chains (designated by “R” in the figure above), which are distinct chemical moieties for each amino acid.

Id. There are typically considered to be 20 naturally occurring amino acids, but many non-naturally occurring amino acids were also known as of the priority date.

See, e.g., id. at 19.

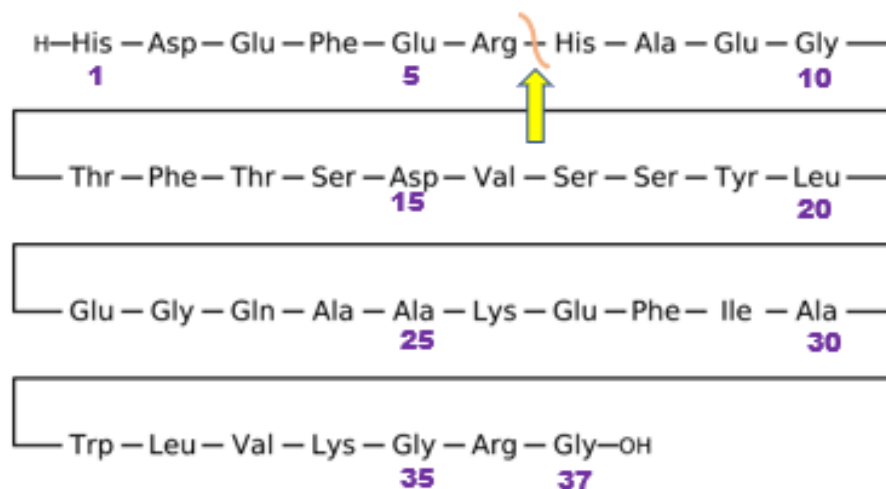
72. Further, amino acids are generally grouped into categories based on the chemical nature of their side chains. *Id.* at 20. Generally speaking, those groups are: (1) nonpolar, aliphatic side chains, (2) aromatic side chains, (3) polar, uncharged side chains, (4) positively charged side chains, (5) and negatively charged side chains. *Id.* at 20-21. Amino acids are often referred to by their single-letter or three-letter abbreviations, rather than their full or chemical names. *Id.* Appendix B summarizes the full names, three letter codes, and single letter codes for amino acids relevant to my declaration.

73. Generally, the number of amino acids present in a peptide chain determines whether it is classified as an oligopeptide (a small number of amino acids), a polypeptide (an intermediate number of amino acids), or a protein (a large number of amino acids, typically more than 50-100). *Id.* at 26. Regardless of size, each amino acid molecule is covalently bound to its neighboring amino acid through “amide” linkages, or peptide bonds, which involve straightforward and simple chemical reactions. *Id.* The following figure demonstrates these peptide bonds (yellow) in a simple peptide containing five amino acids (serine-glycine-tyrosine-alanine-leucine), distinguishable by their side chains (pink). *Id.* at 27.

2. GLP-1 Peptides

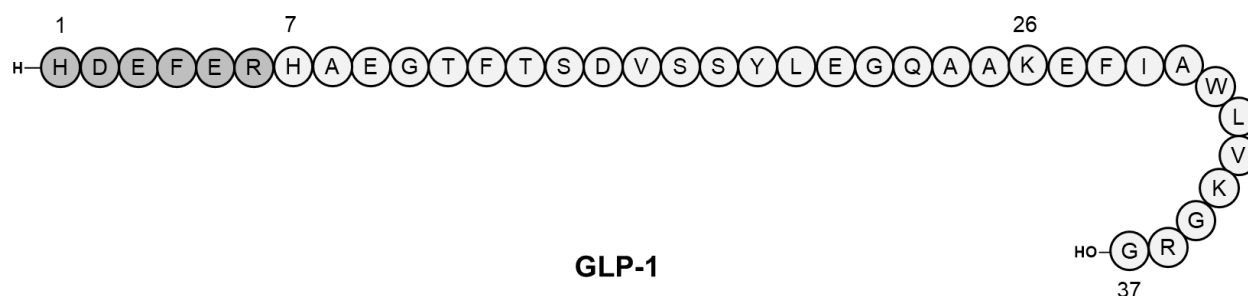
76. With respect to GLP-1, much was known by the priority date of the '343 patent. As discussed above, it was understood that GLP-1 peptides showed promise for the treatment of type-2 diabetes as early as the 1980s. *Supra* Section VII.B.7. In the ensuing decades, POSAs continued to investigate the naturally occurring GLP-1 peptides, which led to the development and optimization of GLP-1 analogues.

77. To explain, native GLP-1 (i.e., the peptide produced by the body) is a peptide containing 37 amino acids⁴:



Native GLP-1(1-37) can also be depicted as follows:

⁴ Image from <https://pubchem.ncbi.nlm.nih.gov/compound/Glucagon-like-peptide-1-1-37> (numbers and shapes added by me) (Ex. 1103).



Native GLP-1 is cleaved following production in intestinal L-cells between Arg⁶ and His⁷ (at the location shown by the yellow above), naturally converting native GLP-1 to its truncated and biologically active forms (i.e., GLP-1(7-37) and GLP-1(7-36)). *See, e.g.*, Ex. 1017 (Drucker 2001) at 4. Thus, GLP-1(7-37) and GLP-1(7-36) were known to be the bioactive forms of native GLP-1 and it was these forms of the molecule that were of interest to researchers. GLP-1(7-37) has the following sequence,⁵ which lacks the amino acids at positions 1-6 in GLP-1(1-37):

⁵ Image from <https://pubchem.ncbi.nlm.nih.gov/compound/16133830> (numbers added by me) (Ex. 1104).

(Mojsov); Ex. 1017 (Drucker 2001). However, it was discovered in the 1990s that GLP-1(7-37) and GLP-1(7-36) suffer from a plasma half-life of about two minutes, meaning they degrade in the body in mere minutes. *See, e.g.*, Ex. 1052 (Orskov) at 1; Ex. 1010 (Knudsen 2004) at 1. This short half-life meant that the naturally occurring GLP-1 peptides were unrealistic drug candidates in their natural form because they would not remain in the body long enough to produce the desired insulinotropic effect. *Id.* Accordingly, as Dr. Knudsen explained, beginning in the 1990s POSAs turned their attention to solving the half-life problem. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 3 (explaining that it was “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*” (emphasis added)); Ex. 1011 (Knudsen 2001) at 1 (“[T]he natural [GLP-1 peptide] is not very useful as a drug ... Thus, in order to make a GLP-1-based drug, one must either make a protracted formulation of the natural hormone, design analogs or derivatives with improved pharmacokinetic properties or find a non-peptide agonist.”); *see also* Ex. 1072 (Deacon) at 1; Ex. 1013 (Dong) at 6; Ex. 1031 (Holz) at Abstract.

79. In the 1990s it was determined that the short half-life of the naturally occurring GLP-1 peptides, like that of GIP, is due to cleavage by the protease enzyme DPP-4. *See generally, e.g.*, Ex. 1075 (Mentlein). Thus, researchers turned their attention to developing GLP-1 analogues that were DPP-4 resistant and would

exhibit a longer half-life and potency suitable for therapeutic use. Indeed, many attempts aimed at developing GLP-1 analogues, or extended action formulations containing naturally occurring GLP-1(7-37) or GLP-1(7-36), were reported. These efforts provided a roadmap for a POSA interested in developing a long-acting GLP-1 analogue suitable for therapeutic use. Moreover, these efforts led to a handful of specific promising GLP-1 analogues.

3. Designing GLP-1 Analogues

80. By the priority date of the '343 patent various studies that assessed the structure-activity-relationship (i.e., "SAR," which involves studying the relationship between the chemical structure of a compound and its biological activity) of the truncated forms of the GLP-1 peptides had been published. *See generally, e.g.*, Ex. 1005 (Adelhorst); Ex. 1017 (Drucker 2001); Ex. 1100 (Holst 2003); Ex. 1031 (Holz); Ex. 1034 (Knudsen 2000); Ex. 1011 (Knudsen 2001); Ex. 1010 (Knudsen 2004). Critically, as explained below, these studies informed a POSA what portions of the GLP-1 peptides *not* to modify.

81. Further, POSAs knew that certain modifications were effective at increasing the half-life of GLP-1 peptides while retaining or enhancing the antidiabetic properties. And as described below, these modifications could be made using commonly employed peptide drug design techniques.

a. Amino acid substitutions at Ala⁸

82. In the early 1990s, Adelhorst disclosed that “side chains in positions 7, 10, 12, 13, and 15 are directly involved in the receptor interaction while positions 28 and 29 are important for GLP-1 to adapt the conformation recognized by the receptor.” Ex. 1005 (Adelhorst) at 1. Thus, from Adelhorst, POSAs knew that the residues at positions 7, 10, 12, 13, 15, 28, and 29 of GLP-1(7-37) could not be modified because they were important to the peptide’s insulintropic effect (i.e., via the receptor interactions).

83. But by the 1990s, as explained above, the mechanisms by which the naturally occurring GLP-1 peptides are degraded were known. *Supra* Section VII.C.2. Specifically, it was known that DPP-4 cleaves the amide bond between residues 8 (Ala) and 9 (Glu) in the naturally occurring GLP-1 peptides, which inactivates the peptide in minutes so that it is no longer able to induce an insulintropic effect. *See, e.g.*, Ex. 1100 (Holst 2003) at 36; Ex. 1075 (Mentlein) at 6. Thus, by the 1990s scientists knew that one approach that may be useful to make a long-lasting GLP-1 analogue would be to confer DPP-4 resistance to the peptide. But scientists were aware that many of the amino acids near the N-terminus (i.e., 7, 10, 12, 13, 15) could not be modified without harming the insulintropic activity of the peptide. *See, e.g.*, Ex. 1005 (Adelhorst) at 1.

84. Scientists had to balance this information as they began making GLP-1 analogues. In other words, POSAs knew that N-terminal modifications would likely be effective at conferring DPP-4 resistance to the peptide. But they also knew that interfering with those N-terminal residues that are critical for the peptide's insulintropic effect would render the peptide less effective. With these competing interests in mind, multiple scientists coalesced around the idea of modifying the amino acid residue at position 8, an alanine, in the GLP-1 peptides. *See, e.g.*, Ex. 1072 (Deacon) at 5 (disclosing that GLP-1 analogues with amino acid substitutions at position 8 “confer resistance to the action of the enzyme DPP IV. Such analogues retain biological activity, and have an improved metabolic stability”); Ex. 1017 (Drucker 2001) at 8 (“Clearly preferred analogues are those which exhibit preserved to enhanced receptor binding concomitant with increased resistance to DP IV-mediated degradation. GLP-1 derivatives with a glycine or α -aminoisobutyric acid at position 8 exhibit both DP IV-resistance and retained binding affinity for the GLP-1 receptor.”); Ex. 1031 (Holz) at 7 (“Typically, these substitutions have been introduced at position 8 of GLP-1 such that the alanine residue is converted to α -aminoisobutyric acid, glycine, serine, or threonine.”); Ex. 1034 (Knudsen 2000) at 4 (“Substitution of glycine instead of alanine at position 8 gives stability toward enzymatic breakdown.”); Ex. 1011 (Knudsen 2001) at 5 (“Amino acid substitutions in position 8 can give better metabolic stability against DPP-IV”).

85. Further studies aimed at other types of chemical modifications at position 8 were unsuccessful. *See, e.g.*, Ex. 1034 (Knudsen 2000) at 3 (“Derivatizing amino acids in the N-terminal part of the peptide, as exemplified [by a GLP-1 analogue acylated with a fatty acid at position 8] led to a substantial loss of potency.”). Thus, POSAs were aware that as far as N-terminal modifications were concerned, an amino acid substitution at position 8 (specifically α -aminoisobutyric acid or glycine) could be used to increase the half-life and retain the potency of the peptide, while adding a substituent at the N-terminus was unlikely to work.

86. Further, as the above references explain, the primary modification that was investigated at position 8 was to substitute non-naturally occurring residues (i.e., not alanine) for alanine. Indeed, this “[a]mino acid substitution” technique was, and remains, a commonly used peptide drug design tool when attempting to make analogues with improved properties (i.e., longer half-life, increased binding affinity or potency, etc.). *See, e.g.*, Ex. 1036 (Lehninger) at 48-49; Ex. 1067 (Sewald) at 172-80.

b. Fatty acid acylation at lysine residues

87. While the N-terminus was an obvious target for modification because of what was known about DPP-4 and the degradation of GLP-1 peptides, POSAs did not limit their efforts to amino acid substitutions or secondary modifications at the N-terminus of GLP-1 peptides. This was primarily because it was discovered that

even with these modifications, the GLP-1 analogues were still cleared rapidly by the kidneys. *See, e.g.*, Ex. 1031 (Holz) at 7; Ex. 1011 (Knudsen 2001) at 1; Ex. 1010 (Knudsen 2004) at 1. Thus, POSAs also investigated mid-chain and C-terminal modifications when attempting to make long-lasting GLP-1 analogues. *See generally, e.g.*, Ex. 1046 ('549 patent); Ex. 1017 (Drucker 2001); Ex. 1030 (Holst 2004); Ex. 1033 (Kim); Ex. 1034 (Knudsen 2000); Ex. 1011 (Knudsen 2001); Ex. 1010 (Knudsen 2004); Ex. 1012 (Knudsen Patent); Ex. 1038 (Markussen).

88. For example, a team of scientists at ConjuChem (a pharmaceutical company) developed a GLP-1 analogue known as "CJC-1131." *See, e.g.*, Ex. 1031 (Holz) at 8; Ex. 1033 (Kim) at Abstract. In addition to containing an amino acid substitution at position 8, CJC-1131 contained a C-terminal modification that enabled it to form a covalent bond to albumin *in vitro*. *See, e.g.*, Ex. 1301 (Holz) at 8; Ex. 1033 (Kim) at 3-4. In particular, CJC-1131 was a GLP-1(7-37) analogue having a D-alanine substitution at position 8 and a lysine residue at position 37 with a 2-[2-[2-maleimidopropionamido(ethoxy)ethoxy]] acetamide (i.e., AEEA-maleimide) substituent. Ex. 1033 (Kim) at 3.

89. As above, the amino acid substitution at position 8 was made to protect the peptide from DPP-4 degradation. *Id.* While this modification was helpful in increasing the half-life, it was the addition of the AEEA-maleimide substituent at the C-terminus that resolved the kidney-clearance issue. *Id.*; *see also* Ex. 1031

(Holz) at 7 (“The two principal strategies rely on conferring DPP IV resistance and reduced plasma clearance of the peptides.”). In fact, because CJC-1131 formed a covalent bond to albumin, it had a half-life of 10-12 days. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 2; Ex. 1030 (Holst 2004) at 5. However, there were concerns that forming a covalent bond to albumin, which is a “permanent” bond, as opposed to some form of non-covalent interaction, which is weaker and can be reversed, could cause antigenic effects or other side-effects. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 4; Ex. 1030 (Holst 2004) at 5.

90. As Kim also showed, POSAs looked at using albumin binding to solve the half-life issue. In fact, this was a long-used approach in peptide drug design. For example, in the 1990s Markussen taught that insulin could be “acylated” (a type of chemical reaction) with a fatty acid to produce insulin analogues with longer half-lives. *See, e.g.*, Ex. 1038 (Markussen) at Abstract. Markussen explained that the “[m]odification of a peptide by fatty acids may be a general method to retard the absorption of the modified peptide from the subcutaneous tissue fluid by an albumin binding mechanism.” *Id.* at 7. This basic technique was naturally extended to GLP-1 peptides. *See, e.g.*, Ex. 1031 (Holz) at 8 (“Fatty acylation confers to each peptide an ability to non-covalently bind via hydrophobic interactions with serum albumin, thereby slowing renal clearance and dramatically extending the circulating half-life.”).

91. Others, like Novo Nordisk and Eli Lilly, later applied this fatty acid acylation technique to make GLP-1 analogues with longer half-lives. For example, before Novo Nordisk developed its series of acylated GLP-1 analogues, Eli Lilly developed a series of acylated GLP-1 analogues, including one known as LY315902, in the early-to-mid-1990s, which had an N-terminal modification, an arginine substitution at position 26 (a lysine in the native peptide), and was acylated with a fatty acid at Lys³⁴. *See, e.g.*, Ex. 1031 (Holz) at 7-8; Ex. 1046 ('549 patent) at 3:35-62. A POSA would have understood that of the amino acids present on native GLP-1(7-37), the lysine residues at positions 26 and 34 had side chains most amenable to an acylation reaction because lysine's primary amine is the strongest nucleophile among the side chains in the GLP-1 backbone. Thus, implementing an Arg²⁶ substitution eliminated the lysine residue (amenable to acylation) at position 26, so only Lys³⁴ would be left to be readily acylated with a fatty acid, making the synthesis simple and easy.

92. Further, Novo Nordisk reported data related to various fatty acid acylated analogues of GLP-1(7-37) in several publications and patents. *See generally, e.g.*, Ex. 1034 (Knudsen 2000); Ex. 1011 (Knudsen 2001); Ex. 1010 (Knudsen 2004); Ex. 1012 (Knudsen Patent). The general takeaway from the Knudsen publications was that fatty acid acylation could be used to make GLP-1 analogues with long half-lives and antidiabetic properties. For example, from

Knudsen 2001, POSAs were aware that “[p]osition 26 or 34 were the most preferred amino acids to derivatize because they were natural lysines and could thus be derivatized easily and without introducing any potential immunogenic changes in the amino acid sequence. Position 26 gave the most potent compound.” Ex. 1011 (Knudsen 2001) at 5. As discussed below, liraglutide contained an arginine substitution at position 34 (a lysine in the native peptide), so the only natural amino acid in liraglutide capable of undergoing an acylation reaction would be Lys²⁶. Thus, Novo Nordisk essentially used the same strategy applied by Eli Lilly earlier (i.e., implementing an arginine substitution at one of the natural lysine residues, leaving only one lysine residue that could be readily acylated), again making the synthesis and chemistry simple and easy.

93. The Knudsen publications also reported important data related to modifications that did *not* work. For example, as above, Knudsen 2000 explained that “[d]erivatizing amino acids in the N-terminal part of the peptide, as exemplified [by a GLP-1 analogue acylated with a fatty acid at position 8] led to a substantial loss of potency.” Ex. 1034 (Knudsen 2000) at 3. Similarly, data related to whether a “linker” or “spacer” moiety was used to attach the fatty acid, the length of the fatty acid, whether a mono- or di-fatty acid was used, and whether the analogue contained multiple fatty acids were reported. *See, e.g.*, Ex. 1034 (Knudsen 2000) at 3; Ex.

1011 (Knudsen 2001) at 4-5; Ex. 1010 (Knudsen 2004) at 2-4; Ex. 1012 (Knudsen Patent) at 192:30-60, 193:35-45.

94. For example, when using a γ -Glu spacer with a *monoacid*, “a significant loss of activity compared to C16 ..., C14..., and C12” was observed. Ex. 1011 (Knudsen 2001) at 4. Further, when *diacid* analogues were prepared *without* a linker or spacer moiety, they “could be no longer than a C14 ... before a loss in potency..., compared to the γ -Glu spacer monoacid series.” *Id.* As another example, Knudsen 2004 explained that “[a]cylation 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 (desaminohistidine) aimed at making the N-terminus more resistant to DPP-IV also destroys potency.” Ex. 1010 (Knudsen 2004) at 3.

95. Finally, as noted above, modifying therapeutic peptides with fatty acids was common as of the priority date of the '343 patent. Indeed, the interactions between fatty acids and albumin were well understood. *See generally, e.g.*, Ex. 1008 (Cistola I); Ex. 1009 (Cistola II); Ex. 1032 (Kenyon); Ex. 1042 (Peters). It was also known that C₁₈ fatty acids formed the strongest non-covalent interactions with albumin. *See, e.g.*, Ex. 1042 (Peters) at 99. And the technology to acylate fatty acids to peptides was routine and automated. *See, generally, e.g.*, Ex. 1036 (Lehninger); Ex. 1067 (Sewald).

c. The use of spacers and/or linkers

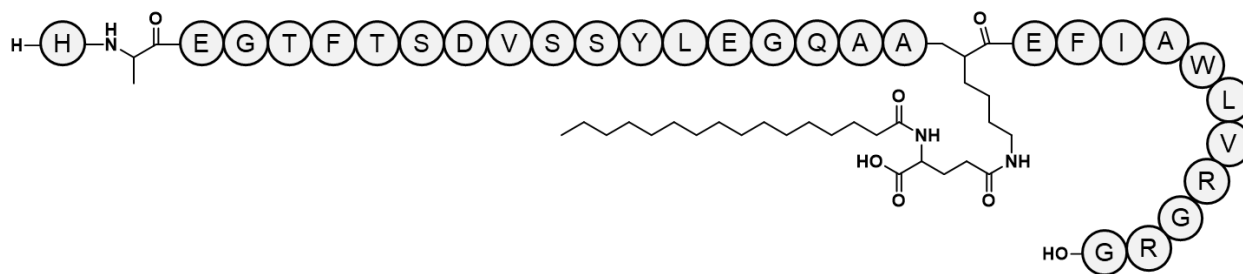
96. As explained above, the acylation of fatty acids to lysine residues of GLP-1 analogues was a well-accepted means to increase the half-life of the peptide. But as the above references also show, the use of “spacer” and/or “linker” moieties to attach said fatty acids was both common and important. Indeed, it was common by the priority date of the ’343 patent to use spacer or linker moieties when preparing peptide analogues generally. *See, e.g.*, Ex. 1067 (Sewald) at 36 (“The synthesis of analogues of bioactive peptides with unusual amino acid building blocks, *linker or spacer molecules* and modified peptide bonds is directed towards the development of potent agonists and antagonists of endogenous peptides.” (emphasis added)); *see also* Ex. 1045 (Sato) at 125:4-8.

97. And in the context of GLP-1 analogues specifically, certain spacers showed up in the art frequently, or were known to have a positive impact on the analogues half-life or antidiabetic properties. For example, the Knudsen publications repeatedly emphasized the importance of a γ -Glu spacer. *See, e.g.*, Ex. 1034 (Knudsen 2000) at 2; Ex. 1011 (Knudsen 2001) at 3-4; Ex. 1010 (Knudsen 2004) at 3. And others in the field recognized the importance of spacers as well. *See, e.g.*, Ex. 1017 (Drucker 2001) at 8; Ex. 1030 (Holst 2004) at 5. Finally, other research groups prepared GLP-1 analogues using a spacer moiety known as [2-(2-

amino)ethoxy)]ethoxy acetic acid (“AEEA”). *See, e.g.*, Ex. 1014 (Bridon) at 3:19-20; Ex. 1033 (Kim) at 3.

4. Liraglutide

98. One of the most promising GLP-1 analogues reported in the literature was Novo Nordisk’s liraglutide (also referred to as NN2211). Liraglutide is an analogue of the naturally occurring human GLP-1(7-37) peptide having the following structure:



See Ex. 1107 (Victoza Label) at Section 11; *see also* Ex. 1031 (Holz) at 7; Ex. 1010 (Knudsen 2004) at 3; Ex. 1011 (Knudsen 2001) at 4-5. As the figure illustrates, liraglutide contains an arginine substitution at position 34 and is acylated with a C₁₆ fatty acid via a γ -glutamic acid (or glutamyl)⁶ spacer at position 26. *See, e.g.*, Ex. 1031 (Holz) at 7; Ex. 1010 (Knudsen 2004) at 3; Ex. 1011 (Knudsen 2001) at 4-5.

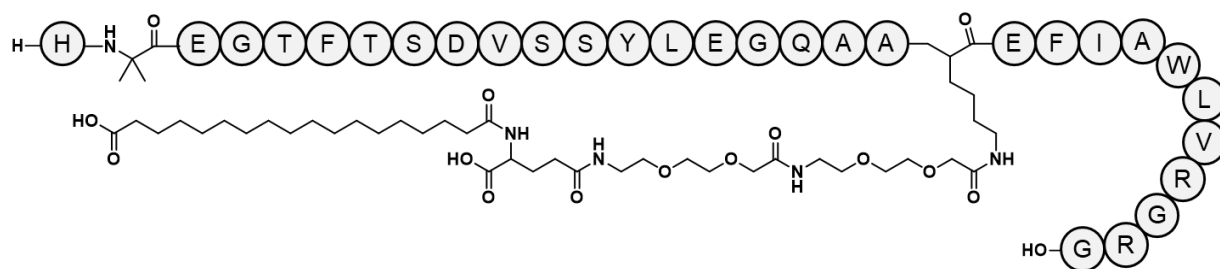
99. Indeed, by the priority date of the '343 patent, Novo Nordisk had completed phase 2 clinical trials with liraglutide in which it was proposed to be a

⁶ I note the γ -glutamyl spacer is present as an (S)-isomer.

once-daily injection compared with twice per day for exenatide (i.e., Byetta). Ex. 1010 (Knudsen 2004) at 3. The data reported for liraglutide plainly showed that it was a very promising GLP-1 analogue in the pipeline. For example, liraglutide was shown to be equipotent to GLP-1 and had a half-life of 11-15 hours, which made it suitable for a once-daily injection. *Id.*; *see also* Ex. 1082 (Edwards); Ex. 1083 (Elbrond); Ex. 1085 (Harder); Ex. 1108 (Holst 2004b); Ex. 1090 (MacDonald); Ex. 1087 (Ribel). The data indicated that liraglutide may even be able to “restore glucose sensitivity to β -cells in patients with type 2 diabetes.” Ex. 1010 (Knudsen 2004) at 5; *see also* Ex. 1080 (Chang); Ex. 1081 (Degn). It was also suggested before the priority date of the ’343 patent that liraglutide (and other GLP-1 peptides) may have additional benefits, including a cardiovascular protecting effect and the ability to lower body weight. *See, e.g.*, Ex. 1011 (Knudsen 2001) at 6; Ex. 1010 (Knudsen 2004) at 5; Ex. 1086 (Larsen). However, there remained a substantial interest in developing additional GLP-1 analogues. In particular, there was a strong desire to develop longer-lasting GLP-1 analogues that retained suitable therapeutic properties. As discussed in detail below, the prior art showed not only which chemical modifications to GLP-1 peptides were promising, but also which ones to avoid.

5. Semaglutide

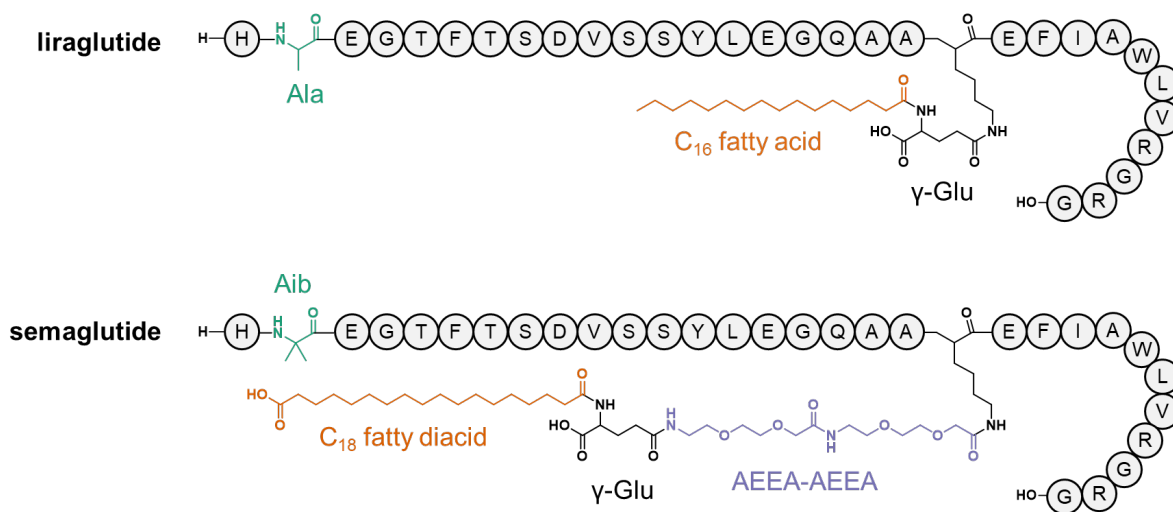
100. As stated above, the challenged claims are directed to semaglutide (and some include its stereoisomer). Semaglutide is a second-generation GLP-1(7-37) analogue developed by Novo Nordisk having the following structure:



See Ex. 1063 (Ozempic Label) at Section 11 (presenting similar structure); *see also* Ex. 1002 ('343 patent) at 61:1-62:37 (Example 4, disclosing the structure and preparation of semaglutide). As shown in the figure above, semaglutide is different from the naturally occurring GLP-1(7-37) peptide in only a few ways. First, it contains two amino acid substitutions: an aminoisobutyric-acid-for-alanine (Aib/Ala) substitution at position 8 (i.e., “Aib⁸”) and, as with liraglutide, an arginine-for-lysine (Arg/Lys) substitution at position 34 (i.e., “Arg³⁴”). Second, the lysine at position 26 is acylated with a C₁₈ fatty diacid via a γ -glutamyl linker (again as an

(S)-isomer), like liraglutide, and a di-8-amino-3,6-dioxaoctanoic acid⁷ (“di-AEEA”) spacer.

101. Thus, in the case of liraglutide, there is an Arg³⁴ substitution and Lys²⁶ is acylated with a C₁₆ fatty acid via a glutamic acid linker. And in the case of semaglutide, there is an Arg³⁴ substitution, an Aib⁸ substitution, and Lys²⁶ is acylated with a C₁₈ fatty diacid via a glutamic acid linker and a di-AEEA spacer. A comparison of liraglutide and semaglutide is shown below (Ex. 1071 (Cooper) shows a similar drawing):



⁷ Several synonyms are used for this chemical compound in the art, including [2-(2-amino)ethoxy]ethoxy acetic acid (i.e., “AEEA”).

(a) Semaglutide meets the limitations of claim 1. I provided claim 1 above, which notes that “the amino acid sequence is that of SEQ ID NO:7.” *Supra* ¶ 38. SEQ ID NO:7 is reproduced below, which sets forth the backbone of semaglutide:

```

<210> SEQ ID NO 7
<211> LENGTH: 31
<212> TYPE: PRT
<213> ORGANISM: artificial
<220> FEATURE:
<223> OTHER INFORMATION: synthetic construct
<220> FEATURE:
<221> NAME/KEY: VARIANT
<222> LOCATION: (2)..(2)
<223> OTHER INFORMATION: Xaa = Aib
<220> FEATURE:
<221> NAME/KEY: MOD_RES
<222> LOCATION: (20)..(20)
<223> OTHER INFORMATION: Lys is substituted

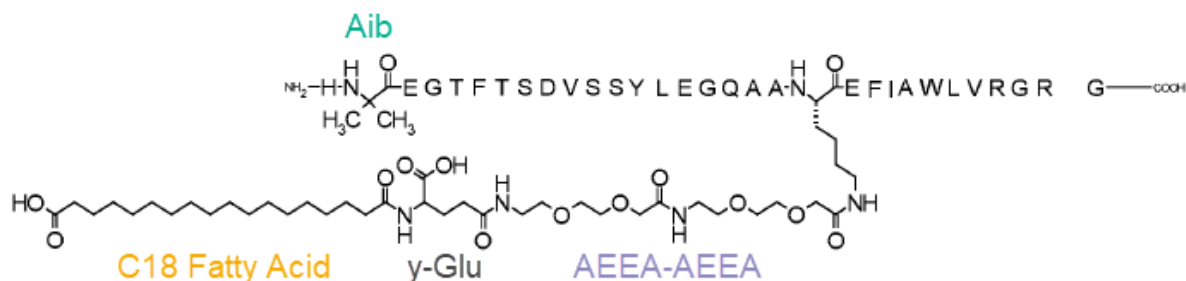
<400> SEQUENCE: 7

His Xaa Glu Gly Thr Phe Thr Ser Asp Val Ser Ser Tyr Leu Glu Gly
1      5      10      15

Gln Ala Ala Lys Glu Phe Ile Ala Trp Leu Val Arg Gly Arg Gly
      20      25      30

```

The chemical structure depicted in (corrected) claim 1, which I have annotated below, shows the fatty acid residue and spacers attached to that backbone:



(b) Accordingly, semaglutide, disclosed in the specification of the '343 patent as Example 4, Ex. 1002 ('343 patent) at 61:1-62:37, meets the limitations of claim 1.

(c) Semaglutide also satisfies the compound element of claim 2 because the same chemical structure and same SEQ ID NO:7 are recited as in claim 1.

(d) Semaglutide also satisfies the compound element of claim 3 because the same chemical structure and same SEQ ID NO:7 are recited as in claim 1.

(e) Semaglutide also satisfies claim 4 because the recited chemical name, which specifies that the γ -Glu compound is present as an "(S)" isomer, is a synonym for semaglutide. In other words, a POSA would understand the chemical nomenclature used in claim 4 describes the chemical structure of semaglutide.

(f) Semaglutide also satisfies the compound element of claim 5 because the same chemical name is recited as in claim 4.

(g) Semaglutide also satisfies the compound element of claim 6 because the same chemical name is recited as in claim 4.

VIII. THE CHALLENGED CLAIMS OF THE '343 PATENT ARE UNPATENTABLE AS OBVIOUS UNDER 35 U.S.C. § 103

A. Scope and Content of the Prior Art

102. I identify below the prior art references supporting my expert opinions on the obviousness of the challenged claims. All the references I cite in this declaration would have been known and publicly available to a POSA as of the

priority date. While I have identified specific references herein, I am also relying generally on the skill, knowledge, and expertise of a POSA based on what was known at the time of the invention, including the knowledge described generally in background references and other statements in this declaration (i.e., without referring to a specific document).

103. The prior art disclosures identified in this declaration would have been understood by a POSA in light of the background knowledge that they would have had by the priority date of the '343 patent. To the extent I list or describe a reference below but do not rely on it as a ground for arguing the challenged claims would have been obvious, that prior art should be understood to form part of the background knowledge of a POSA. These background references also support a POSA's motivation to combine the prior art with a reasonable expectation of success. Further, to the extent I cite a reference for just one or several of its teachings, I reserve the right to rely on that reference for any other aspect of its teaching.

104. For every item of prior art discussed here, I reserve the right to establish that the subject matter described has an earlier effective date or date of first publication than indicated here.

1. Bridon (Ex. 1014)

105. U.S. Patent No. 6,514,500 ("Bridon") is titled "Long Lasting Synthetic Glucagon Like Peptide {GLP-1}" and issued on February 4, 2003. I understand

Bridon is prior art to the '343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the date of the application for patent in the United States.

106. Bridon disclosed “modified insulintropic peptides capable of forming a peptidase stabilized insulintropic peptide.” Ex. 1014 (Bridon) at Abstract. The “modified peptides are administered to treat humans with diabetes.” *Id.* In particular, Bridon disclosed that GLP-1 peptides can be chemically modified to extend their half-lives by linking a maleimide moiety to a lysine residue of the GLP-1 peptide, which enables albumin interactions that extend the half-life of the peptide. *Id.* at 1:10-15. To that end, Bridon taught the use of linking groups, which were defined as “chemical moieties that link or connect reactive groups” (e.g., maleimide) to GLP-1. *Id.* at 3:10-20. One “preferred linking group [was] AEEA ([2-(2-amino)ethoxy)]ethoxy acetic acid).” *Id.* at 3:19-20. Bridon further disclosed GLP-1 peptides containing di-AEEA spacers attached to lysine residues. *See, e.g., id.* at 2:4-13, 28:56-30:67 (Example 5), 31:45-32:22 (Example 7). According to Bridon, the di-AEEA spacers were added to the GLP-1 peptides using automated peptide synthesizers. *Id.* at 14:10-13, 24:5-37.

2. Dong (Ex. 1013)

107. Dong is titled “Glucagon-Like Peptide-1 Analogues with Significantly Improved *in vivo* Activity” and was published in 2001. I understand Dong is prior

art to the '343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the '343 patent.

108. Dong disclosed GLP-1 analogues with “greatly improved plasma half-life and significantly enhanced *in vivo* activity.” Ex. 1013 (Dong) at 6. According to Dong, “[o]ne of the enzymes that are responsible for the fast degradation of GLP-1 *in vivo* is DPP-IV, which cleaves the amide bond between Ala⁸ and Glu⁹ at the N-terminus of hGLP-1.” *Id.* “To prevent this enzymatic cleavage, we replaced Ala⁸ with some unnatural amino acids, including ... aminoisobutyric acid (Aib).” *Id.* Dong explained that Aib is “sterically hindered,” meaning it is bulkier than the alanine residue at position 8, and thus can shield the bond between Ala⁸ and Glu⁹ from DPP-IV. *Id.* These analogues demonstrated “greater DPP-IV resistance” and longer half-lives than native GLP-1 peptides. *Id.*, Table 1. Further, “*in vivo* studies of this new series of hGLP-1 analogues in normal Sprague-Dawley rats demonstrated that the efficacy of the analogues, in terms of the glucose-dependent stimulation of insulin secretion, is highly correlated with their *in vitro* plasma half-life.” *Id.* at 7. As explained below, a POSA would have understood the GLP-1 analogue having only an Aib⁸ substitution to be the most promising analogue reported. *Infra* Section VIII.B.1.b.(i); *see also* Ex. 1013 (Dong) at 6, Table 1.

3. Knudsen 2001 (Ex. 1011)

109. Knudsen 2001 is titled “GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development” and was published in 2001. I understand Knudsen 2001 is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

110. Knudsen 2001 disclosed “a series of GLP-1 derivatives designed for once-daily administration.” Ex. 1011 (Knudsen 2001) at 1. According to Knudsen 2001, “the most optimal pharmacokinetic profile of a GLP-1 drug from this perspective would again be a long half-life with as few as possible peak concentrations. Thus, compounds administered several times a day have a disadvantage over compounds with only once-daily administration.” *Id.* at 3. Knudsen further acknowledged that “[d]erivatizing GLP-1 with long fatty acids has been shown to result in half-lives exceeding 10 h in healthy humans as well as type 2 diabetic patients after [subcutaneous] administration.” *Id.*

111. In particular, Knudsen 2001 explained that:

Fatty acids or fatty diacids, optionally extended with a “spacer” between the epsilon-amino group of the lysine side chain and the carboxyl group of the fatty acid, were used. Acylation with simple fatty acids increases the net negative charge of the resulting molecule with one (by blocking the epsilon-amino group of the lysine), whereas

peptides acylated with a L-glutamoyl-spacer or with diacids provides a further increase of the negative charge. The addition of a negative charge to the acylated molecule is expected to improve solubility at physiological pH.

Id.

112. Further, Knudsen 2001 disclosed that “[m]any different positions in the C-terminal part of GLP-1 could be derivatized with quite long fatty acids ... without affecting the potency.” *Id.* at 4. In contrast, derivatizing GLP-1 peptides in the N-terminal part of the peptide “led to a substantial loss of potency.” *Id.* Knudsen 2001 also admitted that “[a]mino acid substitutions in position 8 can give better metabolic stability against DPP-IV.” *Id.* at 5.

113. Knudsen 2001 concluded that liraglutide (i.e., γ -L-glutamoyl(N- α -hexadecanoyl)-Lys²⁶,Arg³⁴-GLP-1(7-37)) “was selected as the best compound for several reasons.” *Id.* First, the γ -L-Glu spacer “gave the most potent compound.” *Id.* Second, the naturally occurring lysine residues at positions 26 and 34 “were the most preferred amino acids to derivatize because they were natural lysines and could thus be derivatized easily and without introducing any potential immunogenic changes in the amino acid sequence.” *Id.* But Knudsen 2001 further confirmed that derivatizing Lys²⁶ in particular gave the most potent and metabolically stable compound. *Id.* Thus, Knudsen 2001 explained that liraglutide was selected for clinical development. *Id.*

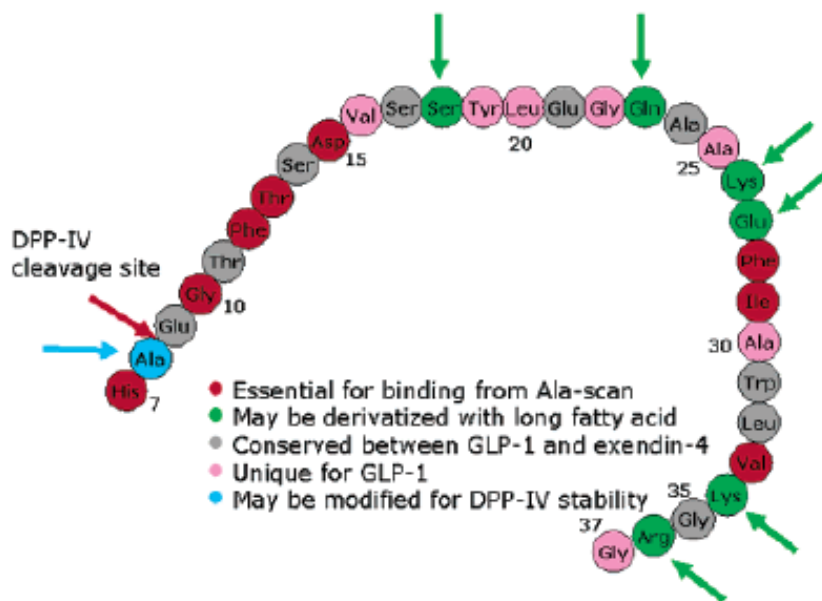
114. Knudsen 2001 also disclosed various clinical data that showed liraglutide to be a promising drug candidate. *Id.* at 5-6. Notably, Knudsen 2001 explained that one study “showed a more pronounced glucose lowering effect of [liraglutide] than exendin-4.” *Id.* at 6. Knudsen 2001 concluded that for a GLP-1 analogue “to be clinically useful the dynamic half-life needs to be significantly prolonged.” *Id.* And while the Knudsen team identified many highly potent GLP-1 analogues derivatized in the C-terminal part of the peptide with short and long fatty acids and amino acid-derived spacers, liraglutide was identified “as a promising new treatment for type 2 diabetes.” *Id.*

4. Knudsen 2004 (Ex. 1010)

115. Knudsen 2004 is titled “Glucagon-like Peptide-1: The Basis of a New Class of Treatment for Type-2 Diabetes” and was published on July 20, 2004. I understand Knudsen 2004 is prior art to the ’343 patent under at least 35 U.S.C. § 102(a) because it was published before the earliest priority date of the ’343 patent. I have been informed that while Knudsen 2004 is § 102(a) prior art, it is possible that Patent Owner could argue it does not qualify as prior art. As discussed below, Knudsen 2004 is a primary reference in Ground 1, but if Knudsen 2004 is not prior art, the challenged claims still would have been obvious for the reasons described in Grounds 2 and 3, which do not rely on Knudsen 2004.

116. Knudsen 2004 disclosed benefits to the GLP-1 class of peptides over other diabetes treatment options and assessed several GLP-1 peptides of interest. *See generally* Ex. 1010 (Knudsen 2004). First, Knudsen 2004 explained that while exendin-4 was also of interest because it may give rise to “more enzymatically stable molecules ... it may then be at the expense of an immune reaction against the peptide.” *Id.* at 3. Further, Knudsen 2004 explained that many early GLP-1 analogues had not “proceeded beyond drug candidates presumably because they are still rapidly cleared by the kidneys and thus require some other form of protraction.” *Id.*

117. Knudsen 2004 also disclosed detailed structure-activity-relationship (“SAR”) information for GLP-1(7-37), summarized in the following figure:



Id. Using this SAR information, Novo Nordisk prepared a series of acylated GLP-1 analogues, including liraglutide. *Id.* According to Knudsen 2004, those acylation studies were conducted to develop GLP-1 analogues “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.” *Id.* Thus, Knudsen 2004 explained that GLP-1 analogues can be prepared using fatty acids and various spacers. *Id.*

118. Further, Knudsen 2004 explained that acylating the N-terminus position 8 reduced the potency by “20 times” and that acylating two fatty acids on both naturally occurring lysines (i.e., at positions 26 and 34), and acylating Lys³⁴ and modifying His⁷, “destroys potency.” *Id.* According to Knudsen 2004, “for acylated derivatives of GLP-1 the SAR is well understood.” *Id.*

119. Knudsen 2004 also disclosed that liraglutide had completed phase 2 clinical trials, where it was proposed as a once-daily injection therapy. *Id.* Knudsen 2004 reiterated what was previously reported in the prior art, namely that liraglutide was equipotent to GLP-1(7-37) and had a “half-life that is more than 10-fold larger [than] that of exendin-4.” *Id.* Knudsen 2004 also disclosed that “[s]everal preclinical and clinical studies” related to liraglutide had been published. *Id.* Finally, Knudsen 2004 explained that liraglutide could produce cardiovascular and

weight loss benefits, and even that it “has been shown to restore glucose sensitivity to β -cells in patients with type 2 diabetes.” *Id.* at 5.

5. Knudsen Patent (Ex. 1012)

120. U.S. Patent No. 6,268,343 (“Knudsen Patent”) is titled “Derivatives of GLP-1 Analogues” and issued on July 31, 2001. I understand the Knudsen Patent is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it issued more than one year before the earliest priority date of the ’343 patent.

121. The Knudsen Patent disclosed various GLP-1 analogues. Ex. 1012 (Knudsen Patent) at Abstract. The Knudsen Patent explained that the GLP-1 analogues should contain as few amino acid substitutions to the naturally occurring GLP-1 peptides as possible. *Id.* at 8:61-9:14. The Knudsen Patent also disclosed that various amino acid substitutions may be used, including non-naturally occurring amino acids, labeled “modified amino acids” in the Knudsen Patent. *Id.* at 10:48-11:33.

122. According to the Knudsen Patent, the GLP-1 analogues “preferably have only one or two [lysine residues] wherein the ϵ -amino group of one or both [lysine residues] is substituted with a lipophilic substituent.” *Id.* at 12:23-26. The Knudsen Patent further indicated that it was preferable for GLP-1 analogues to have only one lysine residue. *Id.* at 12:27-29.

123. The Knudsen Patent disclosed that the purpose of the lipophilic substituent was “[t]o obtain a satisfactory protracted profile of action of the GLP-1 derivative.” *Id.* at 16:57-59. “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.” *Id.* at 16:61-65. “[M]ost preferably,” the GLP-1 analogue contains “one lipophilic substituent.” *Id.* at 16:65-67. Further, the lipophilic substituent could be an “acyl group of the formula $\text{HOOC}(\text{CH}_2)_m\text{CO—}$, wherein m is an integer from 4 to 38,” including “ $\text{HOOC}(\text{CH}_2)_{16}\text{CO—}$.” *Id.* at 19:17-22.

124. According to the Knudsen Patent, “[i]n a most preferred embodiment, the lipophilic substituent is attached—optionally via a spacer—to the ϵ -amino group of a [lysine] residue contained in the parent peptide.” *Id.* at 17:55-57. The Knudsen Patent disclosed several “suitable spacers,” including “succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys.” *Id.* at 17:59-60. This indicated that GLP-1 analogues would tolerate different linkers at this site and that multi-part linkers would work too.

125. One GLP-1 analogue disclosed and claimed in the Knudsen Patent was liraglutide. *See, e.g., id.* at claims 1, 14, 187:41-188:4. While the Knudsen Patent disclosed many GLP-1 analogues, it referred to liraglutide’s favorable properties throughout the patent. First, it disclosed that liraglutide demonstrated a significantly

improved protraction profile (i.e., half-life) that would likely be suitable for a once- or twice-daily dose. *Id.* at 192:30-60 (Table 1, Example 37). Second, it reported efficacy data (via EC₅₀ data) that indicated that liraglutide also retained its antidiabetic properties. *Id.* at 193:35-45. Third, the Knudsen Patent disclosed circular dichroism (“CD”) tests that revealed that “the helix content remains high and essentially independent of the concentration in the 1-200 µM range for [liraglutide] forming partially structured micelle-like aggregates under the same conditions.” *Id.* at 222:19-44, Fig. 1. In other words, the CD tests showed that liraglutide would likely remain in its bioactive conformation at various concentrations, an important property for a drug that is formulated and administered parenterally, and an improvement on native GLP-1(7-37), which suffers from stability issues as concentration increases. However, as the Knudsen Patent acknowledged, liraglutide was likely to suffer from the same aggregation issues that native GLP-1(7-37) was known to suffer from. *Id.* To summarize, the CD tests indicated that there may be challenges getting liraglutide to dissolve and stay in solution, but once in solution it would remain in its bioactive conformation.

126. Another GLP-1 analogue disclosed and claimed by the Knudsen Patent is Arg³⁴Lys²⁶ (N^ε-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH. *Id.* at 177:33-57, Claim 10. This GLP-1 analogue contained an arginine substitution at position 34 (a lysine residue in native GLP-1(7-37)) and was acylated with a C₁₈ fatty diacid at the

lysine residue at position 26 (i.e., Lys²⁶). According to the data in the Knudsen Patent, this GLP-1 analogue exhibited an even longer half-life than liraglutide. *Id.* at 192:30-60, Table 1 (compare Example 11, Arg³⁴Lys²⁶ (N^ε-(ω-carboxyheptadecanoyl))-GLP-1(7-37)-OH, with Example 37, liraglutide). Thus, a POSA would have understood from the Knudsen Patent that using a C₁₈ fatty diacid in lieu of the C₁₆ monoacid used in liraglutide would result in an analogue with a longer half-life than liraglutide.

127. Finally, the Knudsen Patent disclosed that the GLP-1 analogues could be formulated into suitable pharmaceutical compositions and used to treat various disorders, including type-2 diabetes. *Id.* at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18. Liraglutide was formulated in several different pharmaceutical compositions. *Id.* at 216:27-28, 217:23-55, 219:26-45, 220:62-221:20.

6. Additional Prior Art References and Knowledge

128. In addition to the references discussed herein, I utilize the knowledge and expertise of a POSA. All references, whether summarized above or below, that were publicly available prior to the priority date of the '343 patent are within the scope of the prior art. Also, in this declaration I cite the below exemplary references, which inform a POSA's knowledge and demonstrate the state of the art as of the priority date of the '343 patent:

a. Adelhorst (Ex. 1005)

129. Adelhorst is titled “Structure-Activity Studies of Glucagon-like Peptide-1” and was published in 1994. I understand that Adelhorst is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

130. Adelhorst assessed the “function and importance of each amino acid” in GLP-1 by conducting a “systematic exchange of each amino acid in the sequence of GLP-1 by L-alanine or, in the case of L-alanine being the parent amino acid, the amino acid found in the corresponding position of glucagon.” Ex. 1005 (Adelhorst) at 1. Adelhorst found that the “side chains in positions 7, 10, 12, 13, and 15 are directly involved in the receptor interaction while positions 28 and 29 are important for GLP-1 to adapt the conformation recognized by the receptor.” *Id.*

b. Cistola I (Ex. 1008)

131. Cistola I is titled “Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin. I. The Filling of Individual Fatty Acid Binding Sites” and was published in 1987. I understand that Cistola I is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

132. Cistola I described the binding interactions between saturated fatty acids having from 8-18 carbons and albumin. Ex. 1008 (Cistola I) at 1. Cistola I

found that positively charged amino acid residues in albumin interacted with fatty acid carboxyl groups. *Id.* at 7. Using ¹³C NMR, Cistola I provided physicochemical information regarding the order of filling and relative occupation of individual fatty acid binding sites on albumin. *Id.* at 8. In particular, Cistola I reported that the carboxyl group of octadecanoic (or stearic) acid, which contains 18 carbon atoms, interacted with albumin via several high affinity binding sites. *Id.* at Abstract.

c. Cistola II (Ex. 1009)

133. Cistola II is titled “Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin. II. Electrostatic Interactions in Individual Fatty Acid Binding Sites” and was published in 1987. I understand that Cistola II is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

134. Cistola II described the interaction between free fatty acids having 8-18 carbon atoms and albumin. Ex. 1009 (Cistola II) at 1. More specifically, Cistola II disclosed that positively charged side chain residues on albumin had an affinity for, and interacted with, the carboxyl group of fatty acids, including octadecanoic acid. *Id.* at 5.

d. Deacon (Ex. 1072)

135. Deacon is titled “Dipeptidyl Peptidase IV Resistant Analogues of Glucagon-Like Peptide-1 which have Extended Metabolic Stability and Improved

Biological Activity” and was published in 1998. I understand Deacon is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

136. Deacon disclosed four GLP-1 analogues and reported their metabolic stability. Ex. 1072 (Deacon) at Abstract. One GLP-1 analogue reported in Deacon contained an α -aminoisobutyric acid substituent at position 8 on the GLP-1(7-36)amide and GLP-1(7-37) peptides. *Id.* at 2. Deacon disclosed that the Aib⁸ analogues did not degrade “after 6 [hours].” *Id.* at 3. In addition, the Aib⁸ analogues “had similar affinities compared to GLP-1 (7-36) amide” for the GLP-1 receptor and “Aib⁸-GLP-1 (7-36) amide was at least as potent as GLP-1 (7-36) amide in stimulating insulin and inhibiting glucagon secretion.” *Id.* at 4. Deacon concluded that of the four GLP-1 analogues, the Aib⁸ analogue had the highest potency. *Id.* at Abstract (“Aib⁸>Gly⁸>Ser⁸>Thr⁸”).

e. Kenyon (Ex. 1032)

137. Kenyon is titled “¹³C NMR Studies of the Binding of Medium-Chain Fatty Acids to Human Serum Albumin” and was published in 1994. I understand that Kenyon is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

138. Kenyon investigated the interactions of the binding of medium-chain fatty acids to human serum albumin (HSA) using ^{13}C NMR spectroscopy. Ex. 1032 (Kenyon) at 1. Kenyon taught that “[t]he highest affinity sites [on HSA] for both OCT [octanoic] and DEC [decanoic] have properties similar to those of binding sites for longer-chain fatty acids, such as the close proximity of the fatty acid carboxylate to basic amino acid residue(s).” *Id.* Thus, Kenyon disclosed that the carboxylate group of fatty acids bind to and interact with amino acid residues in human serum albumin. *Id.* at Abstract, 3-4.

f. Kim (Ex. 1033)

139. Kim is titled “Development and Characterization of a Glucagon-Like Peptide 1-Albumin Conjugate” and was published in 2003. I understand that Kim is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

140. Kim disclosed biological activity of a developmental GLP-1 analogue known as CJC-1131. Ex. 1033 (Kim) at Abstract. CJC-1131 was a GLP-1(7-37) analogue having a D-alanine substitution at position 8 and a lysine residue at position 37 with a 2-[2-[2-maleimidopropionamido(ethoxy)ethoxy]] acetamide linker. *Id.* at 3. This linker, which included an AEEA group, formed a covalent bond with albumin *in vitro*. *Id.* at 4. This meant that the CJC-1131 peptide would have the same half-life *in vitro* as albumin, which is about 19 days. *Id.* at 4, 8.

g. Knudsen 2000 (Ex. 1034)

141. Knudsen 2000 is titled “Potent Derivatives of Glucagon-like Peptide-1 with Pharmacokinetic Properties Suitable for Once Daily Administration” and was published in 2000. I understand that Knudsen 2000 is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

142. Knudsen 2000 disclosed “[a] series of very potent derivatives of” the truncated GLP-1 peptides. Ex. 1034 (Knudsen 2000) at Abstract. Knudsen 2000 explained that the GLP-1 peptides were “derivatized with fatty acids in order to protract their action by facilitating binding to serum albumin” and that “[m]any of the compounds had similar or even higher potencies” than naturally occurring GLP-1. *Id.*

h. Markussen (Ex. 1038)

143. Markussen is titled “Soluble, Fatty Acid Acylated Insulins Bind to Albumin and Show Protracted Action in Pigs” and was published in 1996. I understand that Markussen is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

144. Markussen taught insulins acylated by fatty acids at the ϵ -amino group of Lys. Ex. 1038 (Markussen) at Abstract. Markussen also explained that “[w]hen

the [negative] charge is moved closer to the fatty acid substitution in Lys^{B29} by deletion of residue Thr^{B30}, the affinity for albumin increases. Possibly, the charge mimics the carboxylate group of a fatty acid and thereby enhances binding to albumin. When the fatty acid is substituted in position Phe^{B1} there is no negative charge in the vicinity, and the binding constant becomes lower by a factor of 4.” *Id.* at 7. Markussen concluded that the “[m]odification of a peptide by fatty acids may be a general method to retard the absorption of the modified peptide from the subcutaneous tissue fluid by an albumin binding mechanism.” *Id.*

i. Peters (Ex. 1042)

145. Peters is titled *Ligand Binding by Albumin* and was published in 1996. I understand that Peters is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the ’343 patent.

146. Peters disclosed various details about albumin, including its structure and ability to interact with compounds. Ex. 1042 (Peters) at 23-33. Peters disclosed that human serum albumin is a protein containing 585 amino acid residues. *See, e.g., id.* at 27, 39. Peters also taught that albumin can interact with a wide spectrum of compounds, including long chain fatty acids (i.e., C₁₆-C₂₀), including various fatty acids having an 18-carbon chain. *Id.* at 93. Peters explained that long-chain fatty acids “bind in a hydrophobic pocket that is adaptable to the ligand, with its negative

charge matched in a salt bond by the positive charge of a nearby lysyl or arginyl residue.” *Id.*

147. Peters also disclosed that stearic acid exhibited stronger binding affinities for albumin than other fatty acids. *Id.* at 99. Further, Peters taught that long-chain fatty acids were known to increase their half-life past their solubility in plasma. *Id.* at 90-93. Accordingly, a POSA would recognize that albumin binds not only to C₁₆ but that a variety of fatty acids would bind it.

j. Sato (Ex. 1045)

148. International Patent Application Publication No. WO 03/74005 (“Sato”) is titled “KDR and VEGF/KDR Binding Peptides and Their Use in Diagnosis and Therapy” and was published on September 12, 2003. I understand Sato is prior art to the ’343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the date of the application for patent in the United States.

149. Sato disclosed chemically modified therapeutic peptides. *See generally* Ex. 1045 (Sato). One chemical modification disclosed in Sato was the use of a di-AEEA spacer to modify certain peptides. *See, e.g., id.* at 22:14-17; *see also id.* at 115-17 (Example 4, Table 10), 124-25 (Experiment B), 145-46 (Table 11), 179-80 (Example 31), 189-90 (Example 37). In particular, Sato specifically disclosed N^ε-substitutions of lysine residues with a di-AEEA spacer and a lipophilic group (e.g.,

a dicarboxylic acid derivative). *See, e.g., id.* at Figures 55, 58, 62, 63. Sato disclosed that the di-AEEA spacer “can be helpful in enhancing binding to target molecule by multiple mechanisms. First, it could help reduce the steric hindrance between [the peptide and its target]. Second, it could provide extra length necessary to reach multiple binding sites available on a single cell.” *Id.* at 125:4-8. Sato also explained that the “[a]ddition of a hydrophilic spacer between the peptide and the group used for attachment to the particle *should routinely be tested* with new targeting molecules as it improved the binding for both of the peptides evaluated here.” *Id.* at 130:30-34 (emphasis added).

k. Sewald (Ex. 1067)

150. Sewald is titled *Peptides: Chemistry and Biology* and was published in 2002. I understand that Sewald is prior art to the '343 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest priority date of the '343 patent.

151. Sewald disclosed general principles related to peptide chemistry and the development of peptide-based drugs. *See generally* Ex. 1067 (Sewald). As Sewald explained:

The synthesis of analogues of bioactive peptides with unusual amino acid building blocks, linker or spacer molecules and modified peptide bonds is directed towards the development of potent agonists and antagonists of

endogenous peptides. Once the amino acids of a protein that are essential for the specific biological mode of action have been revealed, these pharmacophoric groups may be incorporated into a small peptide.

Id. at 36.

152. Sewald also disclosed that peptide analogues were commonly designed using any of several techniques. *See generally* Sewald. For example, peptide analogues were commonly designed using amino acid substitutions, including both naturally occurring and non-naturally occurring amino acids. *See, e.g., id.* at 39. Sewald explained that α -aminoisobutyric acid (i.e., Aib) occurs naturally and was “often incorporated into peptides” in part because it can help stabilize peptides. *Id.* at 179. In addition, it was common to make peptide analogues by modifying the functional groups of amino acid side chains. *Id.* at 39.

B. Ground 1: The Challenged Claims of the '343 Patent Would Have Been Obvious Over Knudsen 2004 in View of the Knudsen Patent, Dong, and Bridon

153. In my opinion, the challenged claims of the '343 patent would have been obvious over Knudsen 2004 in view of the Knudsen Patent, Dong, and Bridon. Below, I explain why the challenged claims would have been obvious in view of these references in the context of a “lead compound” analysis. *Supra* Section II.B. That is to say, I first explain why a POSA would have identified liraglutide as a lead compound and then explain why a POSA would have been motivated to make the

chemical modifications to arrive at semaglutide. In addition, I understand additional experts are offering opinions on behalf of Mylan related to the medicinal chemistry, medical, and formulation aspects of the challenged claims, which are consistent with my opinions below. As above, a POSA here would consult others with relevant expertise and/or work as a team.

1. Claims 1 and 4 of the '343 Patent

154. As explained above, claims 1 and 4 of the '343 patent recite semaglutide, by either its structure or chemical name. *Supra* Sections IV, VII.C.5. It is my understanding if semaglutide would have been obvious, challenged claims 1 and 4 of the '343 patent would have been obvious. Thus, for purposes of my obviousness opinions here, I address only the obviousness of semaglutide.

a. A POSA would have been motivated to select liraglutide as a lead compound and had a reasonable expectation of success

155. I understand that under the lead compound analysis, Mylan must first show that a POSA would have selected a prior art compound, or compounds, as a “lead compound” (i.e., a compound that would be a natural choice for further development efforts). I understand a POSA could identify multiple compounds as “lead compounds” so long as a POSA would have had a reason to select each proposed lead compound.

156. As of the priority date of the '343 patent, POSAs remained motivated to improve on the existing treatments for type-2 diabetes. As detailed above, while a number of diabetes treatment options were available as of the priority date of the '343 patent, many of these classes of drugs had waning interest from the scientific community for various reasons (i.e., serious side effects, short durations of action, etc.) and because other more appealing options began to emerge in the 1990s and early 2000s. *Supra* Sections VII.B.1-6. Most notably, GLP-1 analogues having longer half-lives than the naturally occurring GLP-1 peptides began to emerge as promising new drug candidates for the treatment of type-2 diabetes. *Supra* Section VII.B.7. And POSAs continued to investigate whether GLP-1 analogues having longer half-lives and antidiabetic properties could be developed into a drug suitable for the treatment of type-2 diabetes requiring fewer administrations.

157. Indeed, as of the priority date of the '343 patent, GLP-1-based drugs were considered among the most desirable and interesting drug candidates. *Supra* Section VII.B-C. However, the naturally occurring GLP-1 peptides suffered from extremely short half-lives (i.e., minutes) and it was recognized in the art that chemical modifications would be required to impart a suitable protraction profile to these peptides. *Id.* In my opinion, a POSA motivated to make a GLP-1 analogue having a long protraction profile and desirable antidiabetic properties would have identified liraglutide as a lead compound in view of the prior art, as discussed below.

158. First, Knudsen 2004, authored by the first named inventor on the liraglutide patent from Novo Nordisk, disclosed that liraglutide was a promising GLP-1 analogue. Knudsen 2004 disclosed that liraglutide has the following structure:



Ex. 1010 (Knudsen 2004) at 3. Knudsen 2004 also disclosed that liraglutide was equipotent to naturally occurring GLP-1(7-37) and had a half-life of 11-15 hours, making it suitable for once-daily administration. *Id.* 2-4. Knudsen 2004 additionally disclosed that liraglutide had successfully completed phase 2 clinical trials. *Id.* On this data alone, a POSA interested in developing a GLP-1 analogue would have identified liraglutide as a lead compound worthy of further development.

159. Knudsen 2004 also explained that liraglutide could produce several significant therapeutic benefits beyond its direct antidiabetic effects. For example, Knudsen 2004 disclosed that liraglutide demonstrated cardiovascular and weight loss benefits, and even that it “has been shown to restore glucose sensitivity to β-cells in patients with type 2 diabetes,” indicating the potential to *reverse* progression of type-2 diabetes. *Id.* at 5. These additional therapeutic benefits, and the potential to not only slow disease progression but to reverse it, would have further indicated

to a POSA interested in developing a GLP-1 analogue that liraglutide was a lead compound.

160. Further, Knudsen 2004 explained that GLP-1 analogues generally were superior to other diabetes drugs in several important ways. For example, Knudsen 2004 explained that existing type-2 diabetes drugs suffered from “two major drawbacks ... (1) during their long-term administration body weight increases and (2) the disease progresses over time, also evidenced by an increasing loss of β -cell function.” *Id.* at 1. But as explained above, Knudsen 2004 explained that GLP-1 analogues, including liraglutide, produced the opposite effects—they promoted weight *loss* and could potentially *reverse* disease progression. *See, e.g., id.* at 1-2, 5. In addition, as of the priority date it was thought that “[t]here may be specific receptors in the heart that along with the benefits of reducing blood glucose may protect from cardiovascular complications, and GLP-1 stimulates memory and learning capabilities.” *Id.* at 1.

161. Knudsen 2004 also disclosed that no significant or serious side effects accompanied GLP-1 peptides generally, or liraglutide specifically. *Id.* at 1 (“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.”), 5 (“[S]tudies with [liraglutide] in large-scale clinical trials have not reported such important side effects.”). Thus, Knudsen 2004 concluded that 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.* at 1 (emphasis added).

162. With respect to liraglutide specifically, Knudsen 2004 indicated that it was superior to other GLP-1-based peptides under development at the time. For example, Knudsen 2004 explained that liraglutide had a “half-life that is more than 10-fold larger [than] that of exendin-4.” *Id.* at 3. Knudsen 2004 also explained that exendin-based peptides were less desirable because they were not human-derived peptides and that significant side effects had been reported, including “[a]ntibody formation against exenatide.” *Id.*

163. Knudsen 2004 also noted that CJC-1131, a GLP-1 analogue under development by ConjuChem, was “modified at site 8 to protect against DPP-IV degradation and that [it was] designed to form a covalent bond to albumin after [subcutaneous] injection.” *Id.* at 4. But Knudsen 2004 explained that “[t]he challenge for this approach is perhaps slightly greater than for the others because of the *in vivo* covalent attachment to albumin” and that limited clinical data existed for this peptide. *Id.*

164. Finally, Knudsen 2004 noted that, opposed to liraglutide, whose structure and mechanisms were well understood, little information, and no structural information, existed on certain other compounds in the GLP-1 class that were under investigation at that time. *Id.* at 2, Table 1. Further, Knudsen 2004 explained that earlier attempts at making GLP-1 analogues stable against DPP-4 inhibition were available but that “none of these GLP-1 analogues have proceeded beyond drug candidates presumably because they are still rapidly cleared by the kidneys and thus require some other form of protraction.” *Id.* at 3. In contrast, liraglutide showed that acylating a fatty acid group at Lys²⁶ provided a suitable protraction profile, while retaining the desirable therapeutic properties. *Id.* at 3.

165. Accordingly, in view of Knudsen 2004 alone, a POSA interested in developing a long-lasting GLP-1 analogue would have identified liraglutide as a lead compound. To the extent the Board disagrees that Knudsen 2004 was sufficient to motivate a POSA to use liraglutide as a lead compound, which it was, the state of the art as of the priority date would have cemented a POSA’s choice of liraglutide as a lead compound.

166. For example, the Knudsen Patent repeatedly identified liraglutide’s favorable properties. First, the Knudsen Patent disclosed that liraglutide demonstrated a significantly improved protraction profile (i.e., half-life) that would likely be suitable for a once or twice-daily dose. Ex. 1012 (Knudsen Patent) at

192:30-60 (Table 1, Example 37). Second, it reported efficacy data (via EC₅₀ data) that indicated that liraglutide also retained its antidiabetic properties. *Id.* at 193:35-45. Third, the Knudsen Patent disclosed circular dichroism (“CD”) tests that revealed that liraglutide would remain in its bioactive conformation, even at higher concentrations—an important property for a drug likely to be formulated and administered as a liquid, parenteral product. *Id.* at 222:19-44, Fig. 1.

167. As another example, Knudsen 2001, which on its own also would have motivated a POSA to select liraglutide as a lead compound, *see infra* Section VIII.C.1.a, disclosed that liraglutide “was selected as *the best* compound for several reasons” and that clinical data showed liraglutide to be a promising drug candidate. Ex. 1011 (Knudsen 2001) at 5-6 (emphasis added). Likewise, Knudsen 2000 disclosed that liraglutide (i.e., compound 5 in Table 1) was “very potent” and had a long half-life. Ex. 1034 (Knudsen 2000) at 2. And as noted above, Novo Nordisk published results from a “12-week, double-blind, randomized, controlled trial” that showed “[a] once-daily dose of liraglutide provides efficacious glycemic control and is not associated with weight gain. Adverse events with the drug are mild and transient, and the risk of hypoglycemia is negligible.” Ex. 1055 (Madsbad) at 1. That phase 2 clinical trial involved 193 patients and reinforced with detailed data what was disclosed in the Knudsen Patent, Knudsen 2000, Knudsen 2001, and Knudsen 2004: that liraglutide could be used to treat type-2 diabetes without any

significant side effects. *Id.* at 3 (“The effect of liraglutide increased with duration of treatment”), 4 (reporting that only one patient “experienced minor hypoglycemia” and seven “reported symptoms of hypoglycemia only”), 5 (“improvement of the proinsulin-to-insulin ratio, and thus of β -cell function, would be a desirable effect of a potential new treatment for type 2 diabetes. β -Cell function, as determined by HOMA analysis, was significantly improved at the highest liraglutide dosage compared with placebo”).

168. Finally, other prior art references published by researchers outside of Novo Nordisk recognized liraglutide as one of the most promising diabetes drugs under investigation. *See, e.g.*, Ex. 1031 (Holz) at 6 (“the long lasting GLP-1 derivative [liraglutide] increase[s] β -cell mass in *db/db* diabetic mice”), 6-8 (describing the chemical structure of liraglutide and how they contribute to liraglutide’s properties), 8-11 (noting that liraglutide lowers concentrations of blood glucose in type-2 diabetic patients); Ex. 1073 (Joy) at Abstract (“liraglutide improve[s] glycemic control for patients with type 2 diabetes through unique mechanisms not available with current pharmaceutical products”).

169. Accordingly, in view of Knudsen 2004, and in light of the state of the art, a POSA would have identified liraglutide as a lead compound. While liraglutide appeared to be a suitable candidate for the treatment of diabetes using a once-daily injection, a POSA would have been motivated to develop a GLP-1 analogue

requiring less-frequent administration (i.e., having a longer half-life). Indeed, the '343 patent acknowledged as much. *See* Ex. 1002 ('343 patent) at 1:50-53 (“[T]here is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile.”). This would decrease the risk of patient noncompliance, and would be less burdensome in any event. And although the '343 patent purported to identify this “need,” these efforts were already underway long before the priority date of the '343 patent. *See, e.g.,* Ex. 1033 (Kim) at 3-4; Ex. 1031 (Holz) at 9. Further, I understand Mylan’s medical expert, Dr. Bantle, has opined that this was the case. As explained below, a number of techniques and specific chemical modifications that resulted in GLP-1 peptides having longer half-lives than liraglutide, while retaining desirable therapeutic properties, were already known.

b. A POSA would have been motivated to modify liraglutide to make semaglutide with a reasonable expectation of success

170. As above, a POSA would have been motivated to make a GLP-1 analogue having a long half-life and antidiabetic properties. *Supra* Sections VII.C, VIII.B.1.a. Understanding that liraglutide appeared to have a half-life suitable for once-daily administration, a POSA would have sought to modify liraglutide so that it would have a longer half-life and would require less-frequent administration. As

below, that modification process would have included routine steps that were well known to and understood by POSAs.

171. As a threshold matter, a POSA would have understood that requiring fewer administrations of a diabetes drug would be beneficial to patients. For example, patients would prefer a GLP-1 drug that requires fewer administrations because it would reduce the number of injections and increase compliance. Further, I understand that Dr. Bantle agrees with this and has offered similar opinions on these issues.

172. Additionally, requiring fewer doses could have been beneficial for pharmaceutical manufacturers, offering another, independent, motivation for a POSA to modify liraglutide to have a longer half-life. For example, lower amounts of raw materials might be required to make the product. A manufacturer would need to produce more doses of a product to be administered once-daily compared to a product that could be administered less frequently (i.e., twice-weekly, weekly, bi-weekly, etc.). Thus, for the once-daily product, larger quantities of the chemical compounds (i.e., APIs, excipients, and chemical components required for their synthesis), the dosage pens or vials, and related packaging would be required than for a product that requires less-frequent administration.

173. Further, I understand that Dr. Dalby, Mylan's expert on formulation aspects of the challenged claims, has opined that a POSA would have recognized

that liraglutide could suffer from some formulation-related issues. Indeed, the naturally occurring GLP-1 peptides and their analogues, including liraglutide, were known to suffer from “solubility limitations” that “limit[ed] the usefulness of these compounds, and thus there still [was] a need for improvements in this field.” *See, e.g.,* Ex. 1093 (Flink) at 3:21-24; *see also* Ex. 1012 at 222:19-44, Fig. 1; Ex. 1034 (Knudsen 2000) at 1. Thus, from a pharmaceutical formulation standpoint, a POSA would have been motivated to modify liraglutide to make a GLP-1 analogue with an increased water solubility. As above, this would also be beneficial to pharmaceutical manufacturers because it would make the manufacturing process easier if the drug substance could be readily dissolved and stayed in solution for the duration of the manufacturing process. For this additional reason, a POSA would have been motivated to modify liraglutide in a manner that simultaneously increased its solubility, lengthened its half-life, and retained its suitable therapeutic properties.

174. Accordingly, a POSA would have identified liraglutide as a lead compound. *Supra* Section VIII.B.1.a. And as above, a POSA would have been motivated to modify liraglutide to obtain a longer-lasting GLP-1 drug product that could be dosed less frequently. With this goal in mind, POSAs would have employed their skill and knowledge to apply existing techniques and chemical modifications known in the art to liraglutide specifically. As detailed above, there are only three differences between liraglutide and semaglutide. *Supra* Section

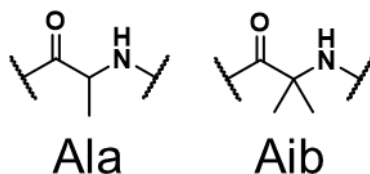
VII.C.4-5. Each of these differences requires only a straightforward modification based on well understood principles in peptide drug design generally, and with respect to GLP-1 analogues specifically, and was motivated by the art described here.

175. In my opinion, semaglutide is merely the result of applying these well-understood modifications and techniques to obtain a GLP-1 analogue that a POSA would have expected to last longer *in vivo* than liraglutide and to exhibit antidiabetic properties. Notably, Novo Nordisk and others in the field disclosed each of these techniques and modifications in the prior art when describing how to design long-lasting GLP-1 analogues. I address each of these modifications below.

(i) A POSA would have been motivated to perform an Aib⁸ substitution with a reasonable expectation of success

176. Semaglutide has a different amino acid residue at position 8 on the peptide chain than liraglutide. *Supra* Sections VII.C.4-5. Liraglutide has an alanine at position 8, which is the same amino acid found in naturally occurring GLP-1(7-37). *Supra* Section VII.C. In semaglutide, an aminoisobutyric acid residue is substituted for the alanine at position 8. *Supra* Section VII.C.5. In view of Dong, and considering a POSA's knowledge of the state of the art, a POSA would have been motivated to make this amino acid substitution and would have reasonably expected the resulting peptide to have a longer half-life and antidiabetic properties,

or considered it obvious to try. Aib was both taught by the prior art and is nearly identical to the native Ala residue, and so would have been attractive as a very conservative modification:



177. According to Dong, “[o]ne of the enzymes that are responsible for the fast degradation of GLP-1 *in vivo* is DPP-IV, which cleaves the amide bond between Ala8 and Glu9 at the N-terminus of hGLP-1.” Ex. 1013 (Dong) at 6. Dong explained that Aib is a “sterically hindered amino acid[],” which “make[s] the peptide bond between positions 8 and 9 less accessible to the enzyme, yielding analogues with greater DPP-IV resistance.” *Id.* Dong therefore “replaced Ala8 with some unnatural amino acids, including ... aminoisobutyric acid (Aib).” *Id.* These analogues, including [Aib⁸]hGLP-1(7-36)NH₂, demonstrated “greater DPP-IV resistance” and significantly longer half-lives than native GLP-1 peptides. *Id.*, Table 1. Further, “*in vivo* studies of this new series of hGLP-1 analogues in normal Sprague-Dawley rats demonstrated that the efficacy of the analogues, in terms of the glucose-dependent stimulation of insulin secretion, is highly correlated with their *in vitro* plasma half-life.” *Id.* at 7. Thus, Dong expressly disclosed that substituting an

Aib residue for Ala at position 8 would result in a GLP-1 analogue having a longer half-life while *enhancing* the antidiabetic properties of the peptide.

178. Dong also reported half-life and efficacy-related data for seven other GLP-1 analogues, including [Aib^{8,35}]hGLP-1(7-36)NH₂ (i.e., Compound 4, a GLP-1 analogue having Aib substitutions at positions 8 and 35). *Id.* at 6. Dong explained that this Aib^{8,35} analogue

enhanced the insulin response to elevated glucose with a calculated ED₅₀ at 16.0 pmol/kg, compared to that of the native hGLP-1(7-36)NH₂ at 121 pmol/kg. This 7.6-fold increase in efficacy is likely due to its enhanced enzymatic stability, resulting in an increased circulating half-life. In studies utilizing the *db/db* mouse, intraperitoneal administration of compound 4 at 5–50 nmol/kg to 5-week old animals produced a dose-dependent reduction in blood glucose monitored over a 5-h period.

Id. at 7. Indeed, it was the Aib^{8,35} analogue that Ipsen Biopharmaceuticals elected to take into clinical trials. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 4.⁸ Thus, as of the

⁸ As noted by Knudsen 2004, Ipsen had not expressly identified BIM-51077 by its chemical structure as of the priority date. But the Dong research group had published the relevant data and identified it as a “representative analogue” well before the priority date. Ex. 1013 (Dong) at 7.

priority date, a research group having no relationship with Novo Nordisk or the inventors of the '343 patent was simultaneously pursuing GLP-1 analogues having Aib substitutions at select amino acid residues. In my opinion, this further demonstrates that a POSA would have been motivated to make an Aib amino acid substitution at position 8 and would have reasonably expected the resulting analogue to have a longer half-life.

179. Further, in my opinion, the data presented in Dong suggest that [Aib⁸]hGLP-1(7-36)NH₂ (i.e., Compound 3, having only one Aib substitution, at position 8) would have been a better drug candidate than the Aib^{8,35} analogue. For example, compare the K_i (i.e., the “inhibition constant,” or the inhibitor’s “dissociation constant”) values for Compound 3 (the Aib⁸ analogue) and Compound 4 (the Aib^{8,35} analogue) reported in table 1:

Table 1. hGLP-1 receptor binding affinity and rat plasma half-life.

Peptide	hGLP-1 ^a K _i (nM)	Rat plasma T1/2 (h)	Sequence
hGLP-1(7-36)NH ₂	1.09	0.84	
1	1.13	4.35	[N-Me-D-Ala ⁸]hGLP-1(7-36)NH ₂
2	7.23	4.86	[A5c ⁸]hGLP-1(7-36)NH ₂
3	0.64	4.52	[Aib ⁸]hGLP-1(7-36)NH ₂
4	0.95	9.76	[Aib ^{8,35}]hGLP-1(7-36)NH ₂
5	1.26	8.34	[Aib ⁸ ,β-Ala ³⁵]hGLP-1(7-36)NH ₂
6	1.39	17.6	[Aib ^{8,35} ,Phe ³¹]hGLP-1(7-36)NH ₂
7	1.77	7.40	[Aib ⁸ ,Phe ³¹ ,β-Ala ³⁵]hGLP-1(7-36)NH ₂
8	2.12	8.91	[Aib ^{8,35} ,Arg ^{26,34} ,Phe ³¹]hGLP-1(7-36)NH ₂

^a The assays were done in CHO-K1 cells expressing the human recombinant GLP-1 receptor.

Id. at 6 (orange boxes added for emphasis). The inhibition constant refers to the concentration of a peptide required to produce half maximum inhibition. In other words, a lower inhibition constant indicates that a smaller amount of the peptide would be required to bind to the receptor of interest (here, e.g., the GLP-1 receptor). Thus, a lower K_i suggests a potentially more potent and efficacious peptide.

180. As can be seen in Table 1 of Dong, the Aib⁸ analogue had a significantly lower K_i than all other analogues, including the Aib^{8,35} analogue, as well as the naturally occurring GLP-1 peptide. *Id.* Thus, in my opinion a POSA would have understood the data from Dong to suggest that the Aib⁸ analogue would actually be a *more* potent and efficacious analogue than the other analogues, including the Aib^{8,35} analogue. While the Aib^{8,35} analogue had a longer half-life than the Aib⁸ analogue, it still fell well short of the half-life of liraglutide. *Supra* Section VIII.B.1.a.

181. Accordingly, in my opinion, a POSA would have been motivated to modify liraglutide with an Aib⁸ amino acid substitution in view of Dong, or considered it obvious to try. Dong expressly taught that an Aib⁸ amino acid substitution “yield[ed] [an] analog[] with greater DPP-IV resistance” and significantly stronger receptor binding. Ex. 1013 (Dong) at 6. A POSA would have reasonably expected these improved properties to be incorporated into a modified liraglutide peptide, which does not otherwise have any N-terminal modifications. In

other words, a POSA would have expected an Aib⁸ substitution to liraglutide to result in enhanced DPP-4 resistance (i.e., a longer half-life) and improved receptor binding (i.e., a potentially more efficacious drug). Further, a POSA would have recognized that while the Aib⁸ substitution would complement and work synergistically with liraglutide's properties, it could not replace the fatty acid-acylation technique used to extend the half-life of liraglutide. *Infra* Section VIII.B.1.iii.

182. Additionally, Knudsen 2004, the primary reference in Ground 1, specifically called out residue 8 as a site that “[m]ay be modified for DPP-IV stability.” Ex. 1010 (Knudsen 2004) at 3, Fig. 3. Knudsen 2004 also acknowledged that others in the field were exploring modifications “at site 8 to protect against DPP-IV degradation.” *Id.* at 2, 4. Similarly, the Knudsen Patent explained that while GLP-1 analogues should contain as few amino acid substitutions to the naturally occurring GLP-1 peptides as possible, various amino acid substitutions may be used, including non-naturally occurring amino acids. Ex. 1012 (Knudsen Patent) at 8:61-9:14, 10:48-11:33. Accordingly, when Knudsen 2004 is read in view of Dong and the Knudsen Patent (i.e., three of the references relied on in Ground 1), a POSA would have understood that an Aib⁸ substitution would have resulted in a GLP-1 peptide with a longer half-life than liraglutide and that minimizing the number of amino acid substitutions would be preferred.

183. Additionally, the state of the art generally and a POSA's knowledge would have further confirmed that a POSA would have been motivated to make this modification to liraglutide with a reasonable expectation of success. *Supra* Section VII.C.3.a. For example, it was previously reported in the art that Aib⁸ analogues impart DPP-4 protection (i.e., a longer half-life) and enhance antidiabetic properties. For example, Deacon, published in 1998 and authored by scientists from Novo Nordisk, disclosed that Aib⁸ analogues did not degrade "after 6 [hours]." Ex. 1072 (Deacon) at 3. In addition, the Aib⁸ analogues "had similar affinities compared to GLP-1 (7-36) amide" for the GLP-1 receptor and "Aib⁸-GLP-1 (7-36) amide was at least as potent as GLP-1 (7-36) amide" and superior to other position 8 substitutions "in stimulating insulin and inhibiting glucagon secretion." *Id.* at 4. Thus, a POSA would have understood that of the analogues disclosed in Deacon, only the Aib⁸ analogue exhibited insulin output over basal conditions.

184. In addition, other prior art references also recognized that Aib⁸ substitutions were promising. *See, e.g.*, Ex. 1031 (Holz) at 7; Ex. 1017 (Drucker 2001) at 8; Ex. 1047 (Buckley) at 25:17-30, Fig. 1. Further, general peptide chemistry references recognized that it was not uncommon for Aib to appear in peptide or protein sequences. *See, e.g.*, Ex. 1067 (Sewald) at 49, 179. Finally, a POSA would have understood that performing amino acid substitutions in peptide drug development was a commonly employed technique that required a routine level

of skill by the priority date. *See, e.g., id.; see also supra* Section VII.C.3.a. The same was true for an Aib substitution specifically—there was nothing unique or challenging about substituting an Aib residue for an Ala residue, which could be performed using automated technology by the priority date.

185. Accordingly, in my opinion, a POSA would have been motivated to modify liraglutide with an Aib⁸ amino acid substitution in view of Dong, as well as Knudsen 2004 and the Knudsen Patent, and would have reasonably expected the resulting peptide to have a longer half-life while retaining its antidiabetic properties. Indeed, it was well understood in the art that this Aib⁸ substitution would extend the half-life of GLP-1 analogues.

186. Further, this combination of references would have motivated a POSA to make only this one additional amino acid substitution to liraglutide (i.e., in addition to the Arg³⁴ substitution already present in liraglutide). As the Knudsen Patent stressed, a POSA would have been motivated to minimize the number of amino acid substitutions made to the native GLP-1 (7-37) peptide. Ex. 1012 (Knudsen Patent) at 8:61-9:14. It was also common in the art to minimize the number of amino acid substitutions, and to make conservative amino acid substitutions (like the Aib⁸ and Arg³⁴ substitutions here), to avoid the risk of harming the peptide's bioactivity or causing adverse side effects. Ex. 1014 at 6:49-59; *see also* Ex. 1036 (Lehninger) at 49. Further, Knudsen 2004 disclosed detailed SAR

data indicating that *only* position 8 “[m]ay be modified for DPP-IV stability.” Ex. 1010 at 3, Fig. 3. Accordingly, a POSA would have been motivated to modify liraglutide, which already contained an Arg³⁴ substitution for the reasons discussed above, *supra* Section VII.C.3.b, with an Aib⁸ substitution (to impart DPP-IV stability) and no other amino acid substitutions.

187. However, a POSA would not have stopped there, as detailed below. A POSA would have been motivated to use additional known techniques and modifications (i.e., modifications other than amino acid substitutions) to make an effective GLP-1 analogue having a half-life significantly longer than liraglutide.

**(ii) A POSA would have been motivated
to use a di-AEEA spacer with a
reasonable expectation of success**

188. The second difference between liraglutide and semaglutide is the use of a di-AEEA “spacer” to connect the glutamic acid linker and fatty acid to Lys²⁶ in semaglutide. However, liraglutide contained a fatty acid that was bound to Lys²⁶ via a glutamic acid linker. Thus, the only difference was the use of a di-AEEA spacer. *Supra* Sections VII.C.4-5. In view of Bridon, and a POSA’s knowledge of the state of the art, a POSA would have been motivated to use a di-AEEA spacer and would have reasonably expected the resulting peptide to have a longer half-life and better antidiabetic properties, or considered it obvious to try.

189. Bridon explained that linking groups (i.e., “chemical moieties that link or connect reactive groups to [peptides]”) could be used both as a general tool in peptide drug design and to modify GLP-1 peptides specifically. Ex. 1014 (Bridon) at 3:10-20. One “preferred linking group” was the AEEA moiety later used in semaglutide. *Id.* at 3:19-20. Further, Bridon explained that these linking groups could be easily bound to the peptide using basic, automated synthetic technologies available at the time. *See, e.g., id.* at 14:10-13; 24:5-37.

190. In addition, Bridon disclosed that the di-AEEA spacer could serve as a means to link a maleimide moiety to the GLP-1 peptide, which would interact with albumin to extend the half-life of the peptide. *See, e.g., id.* at 28:56-30:67 (Example 5), 31:45-32:22 (Example 7). Bridon expressly disclosed the use of a di-AEEA spacer in GLP-1 analogues with a goal of producing a peptide having a longer half-life. *See, e.g., id.* at Abstract, 4:35-63, 28:56-30:67 (Example 5), 31:45-32:22 (Example 7). In each of these examples, the di-AEEA spacer was bound to a lysine residue at position 37 using automated peptide synthesis. *Id.* at 28:56-30:67 (Example 5), 31:45-32:22 (Example 7).

191. Accordingly, Bridon taught that a di-AEEA spacer could easily be attached to a lysine residue of a GLP-1 peptide. Further, Bridon demonstrated that a di-AEEA moiety could be used as a “spacer” between the GLP-1 peptide and the albumin binding component, in this case a maleimide moiety. Thus, because

liraglutide has only one lysine residue (i.e., Lys²⁶) to which the di-AEEA spacer could readily be acylated, *supra* Section VII.C.3.b, and in view of a POSA's knowledge of the state of the art discussed below, a POSA would have been motivated to modify liraglutide by inserting a di-AEEA spacer between the glutamic acid linker-fatty acid moiety and the GLP-1 peptide chain at Lys²⁶. Further, a POSA would have had a reasonable expectation of success in making the peptide because Bridon disclosed that the peptide could be synthesized using automated synthetic techniques. Additionally, a POSA would have reasonably expected the GLP-1 analogue to have an extended half-life in view of Bridon, which showed that the di-AEEA spacer would not negatively impact albumin binding.

192. Additionally, Knudsen 2004 disclosed that the acylation technique used in liraglutide was “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.” Ex. 1010 (Knudsen 2004) at 3. Thus, Knudsen 2004 explained that GLP-1 analogues can be prepared using fatty acids and various spacers (or linkers) with the goal of binding to albumin as a means to extend the half-life of the peptide, much like the technique disclosed in Bridon. Further, while Knudsen 2004 disclosed that liraglutide used a glutamic acid linker (analogous to the term “spacer” in the art), it also acknowledged that

“[s]pacers other than [glutamic acid] can be used.” *Id.* Knudsen 2004 went on to acknowledge that CJC-1131, the GLP-1 analogue claimed in Bridon having an AEEA spacer, was “modified at site 8 to protect against DPP-IV degradation and [was] designed to form a covalent bond to albumin.” *Id.* at 4; *see also id.* at 2, Table 1. Indeed, Knudsen 2004 acknowledged that CJC-1131 was reported to have a very long half-life. *Id.*

193. Similarly, the Knudsen Patent disclosed that “[i]n a most preferred embodiment, [a] lipophilic substituent is attached—optionally via a spacer—to the ϵ -amino group of a [lysine] residue contained in the parent peptide.” Ex. 1012 (Knudsen Patent) at 17:55-57. The Knudsen Patent disclosed several “suitable spacers,” including “succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys.” *Id.* at 17:59-60. This indicated that GLP-1 analogues would tolerate other linkers at this site and that multi-part linkers would work too. The Knudsen Patent again confirmed that while the glutamic acid linker is important, it could be modified or extended with additional compounds.

194. Accordingly, when Knudsen 2004 is read in view of Bridon and the Knudsen Patent (i.e., three of the references relied on in Ground 1), a POSA would have understood that modifying liraglutide with a di-AEEA spacer at Lys²⁶ would result in a GLP-1 analogue having a long half-life, particularly where an Aib⁸ substitution was also made, while retaining the antidiabetic properties of the peptide.

For these additional reasons, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer at Lys²⁶ and would have had a reasonable expectation of success.

195. Additionally, a POSA would have understood based on their knowledge of the state of the art generally that spacers, including AEEA-based spacers, were commonly used in peptide synthesis and design. Indeed, several other references also disclosed that the AEEA spacer compound could be used in the context of GLP-1 analogue design.

196. For example, Kim, authored by many of the listed inventors of Bridon, disclosed that CJC-1131 contained an AEEA spacer at Lys³⁷. Ex. 1033 (Kim) at 3. Kim further disclosed that CJC-1131 exhibited a half-life commensurate with that of albumin's own half-life, while retaining the desired antidiabetic properties. *See generally* Ex. 1033 (Kim). A POSA would have understood from Kim that an AEEA spacer does not negatively impact albumin binding, particularly because the maleimide group is a relatively small functional group (i.e., compared to the long fatty acid used in liraglutide and semaglutide) and thus little space would exist between albumin (which binds to maleimide) and the AEEA spacer. Further, Kim taught that the AEEA moiety generally would not negatively affect the efficacy of a GLP-1 analogue. *Id.* at 3.

197. In addition, Sato disclosed the use of spacers as a general technique that could be used to design therapeutic peptides. *See generally* Ex. 1045 (Sato). Sato explained that the “[u]se of such linkers/spacers may improve the relevant properties of the binding peptide (e.g., increase serum stability, etc.).” *Id.* at 55:6-7. In particular, Sato disclosed the use of a di-AEEA spacer to modify certain peptides. *See, e.g., id.* at 22:14-17; *see also id.* at 115-17 (Example 4, Table 10), 124-25 (Experiment B), 145-46 (Table 11), 179-80 (Example 31), 189-90 (Example 37). Sato specifically disclosed N^ε-substitutions of lysine residues with a di-AEEA spacer and a lipophilic group (e.g., a dicarboxylic acid derivative). *See, e.g., id.* at Figures 55, 58, 62, 63.

198. Finally, Sato disclosed that the use of a di-AEEA spacer enhanced binding of certain peptides to their targets. *See, e.g., id.* at 124:24-125:8, 128:5-13, 179:1-180:28. Sato explained that the di-AEEA spacer “can be helpful in enhancing binding to target molecule by multiple mechanisms. First, it could help reduce the steric hindrance between [the peptide and its target]. Second, it could provide extra length necessary to reach multiple binding sites available on a single cell.” *Id.* at 125:4-8. Sato also explained that the “[a]ddition of a hydrophilic spacer between the peptide and the group used for attachment to the particle *should routinely be tested* with new targeting molecules as it improved the binding for both of the peptides evaluated here.” *Id.* at 130:30-34 (emphasis added).

199. Thus, Sato disclosed both that spacers could be used in peptide drug design generally, and that the di-AEEA spacer specifically offered a number of potential benefits. Most notably, Sato disclosed that the di-AEEA spacer enhanced the properties of the peptides, particularly their stability and possibly their efficacy (via enhanced receptor binding).

200. As the above references explained, the use of spacers in peptide drug design was common practice by the priority date of the '343 patent. Indeed, general textbooks at the time also confirmed this to be true. For example, Sewald explained:

The synthesis of analogues of bioactive peptides with unusual amino acid building blocks, *linker or spacer molecules* and modified peptide bonds is directed towards the development of potent agonists and antagonists of endogenous peptides. Once the amino acids of a protein that are essential for the specific biological mode of action have been revealed, these pharmacophoric groups may be incorporated into a small peptide.

Ex. 1067 (Sewald) at 36 (emphasis added).

201. As explained above, Knudsen 2004 disclosed detailed SAR information, and explained which amino acids of the naturally occurring GLP-1 peptide were “essential for binding.” Ex. 1010 (Knudsen 2004) at 3. Thus, a POSA would have turned to commonly used techniques to modify liraglutide, including the use of linkers or spacer molecules. As the references above show, the di-AEEA

spacer in particular was used to modify peptides and had in fact been known since about 1980. *See generally* Ex. 1043 (Rando). Further, it was hypothesized in the art that liraglutide could be *improved* by using a longer spacer moiety. *See, e.g.*, Ex. 1030 (Holst 2004) at 5 (“The apparent retention of high biological activity in spite of the presence of the albumin moiety contrasts strikingly to [liraglutide], the intrinsic activity of which is clearly lowered by albumin binding (by ~2–3 orders of magnitude), suggesting that the site of attachment to albumin is of importance and that *the linker position and length in 2211 could be suboptimal.*” (emphasis added)).

202. Accordingly, a POSA would have been aware of these general teachings in the art, which further demonstrate that a POSA would have motivated to modify liraglutide with a di-AEEA spacer and would have had a reasonable expectation of success. In my opinion, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer at Lys²⁶ in view of Bridon. This is reinforced by the state of the art and general understanding of a POSA as of the priority date of the ’343 patent. Indeed, a POSA would have understood the di-AEEA spacer would contribute additional desirable properties to the GLP-1 analogue because of its chemical nature.

203. For example, a POSA would have understood that the di-AEEA spacer would have increased the physical space between the fatty acid and the peptide chain. *See, e.g.*, Ex. 1045 (Sato) at 125:4-8. A POSA would have understood that

this would allow for the fatty acid to interact with albumin, a much larger and bulkier protein than the GLP-1 peptide, but at a greater distance from the GLP-1 peptide than in liraglutide (which only contained a glutamic acid linker). In other words, by adding the di-AEEA spacer, albumin would be further away from the peptide and would be less likely to block (physically or chemically) the amino acids known to be essential for interacting with the GLP-1 receptor. Both albumin and the GLP-1 receptor are bulky, and they are significantly larger. Albumin is about 66.5 kDa⁹ and the GLP-1 receptor is similarly sized.¹⁰ Liraglutide is about 3.7 kDa (approximately 18 times smaller). Ex. 1012, 187:41-188:4. By way of comparison, if liraglutide were a passenger vehicle (like a Ford F-150),¹¹ albumin would be a commercial airliner (like a Boeing 737).¹² A POSA would reasonably conclude that use of a spacer to separate the binding sites of albumin and the GLP-1 receptor could

⁹ Ex. 1098 (Nicholson).

¹⁰ Ex. 1097 (Göke).

¹¹ Ex. 1101, <https://www.caranddriver.com/ford/f-150> (giving weight range of 5562-5794 lb).

¹² Ex. 1102, <https://modernairliners.com/boeing-737/boeing-737-specifications/> (giving weight range of 97516-115520 lb).

allow for stronger binding between the peptide and the GLP-1 receptor, thus potentially increasing the potency of the peptide.

204. In addition, because AEEA has a neutral charge but has several polar groups, a POSA would have understood that the addition of a di-AEEA spacer while retaining the glutamate linker would increase the molecule's hydrophilicity and maintain its negative charge. A POSA would have understood this to be important for at least two reasons. First, it would increase the polarity of the peptide, making it more hydrophilic than liraglutide. *See, e.g.*, Ex. 1043 (Rando) at 1 (describing AEEA as a “hydrophilic spacer group”). This means the modified analogue would be easier to dissolve in water and would be less susceptible to formulation and manufacturing issues. Indeed, Knudsen 2000 suggested this would be the case. Ex. 1034 (Knudsen 2000) at 2 (disclosing that the “extra negative charge added to the acylated molecule is also expected to provide a higher solubility at physiological pH”).

205. Second, it was suggested in the art that the addition of a carboxylate group near a fatty acid on a peptide could enhance albumin binding, and the modification would retain the glutamate carboxylate group near the fatty acid. *See, e.g.*, Ex. 1038 (Markussen) at 7 (“Possibly, the charge mimics the carboxylate group of a fatty acid and thereby enhances binding to albumin. When the fatty acid is substituted in position Phe^{B1} there is no negative charge in the vicinity, and the

binding constant becomes lower by a factor of 4.”). And Knudsen 2000 confirmed this to be true. Ex. 1034 (Knudsen 2000) at 2 (disclosing that “[a]cylation with simple fatty acids increases the net negative charge of the resulting molecule by 1, whereas peptides acylated with a L-glutamoyl spacer or with diacids provide a net increase of the negative charge by 2. In the two latter cases, an enhanced effect on binding to albumin is predicted.”). In view of the additional properties that the spacer would add to the peptide, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer at Lys²⁶.

206. Finally, I understand two of Mylan’s other experts, Drs. Dalby and Soares, have opined that a POSA would have been motivated to use a di-AEEA spacer for additional reasons. Because a POSA would collaborate with these individuals (i.e., a formulator like Dr. Dalby and a medicinal chemist like Dr. Soares), the motivations provided by others would have given a POSA additional motivations to pursue this modification. While I understand that each of their declarations provide detailed reasons for their opinions, I understand they are providing the following motivations generally.

207. As to Dr. Dalby, I understand he is offering the opinion that a formulator would have been motivated to use a di-AEEA spacer because they would have reasonably expected it to make the peptide easier to formulate. In particular, I understand Dr. Dalby opines that a POSA would have understood that the di-AEEA

spacer would have increased the negative charge and polarity of the peptide, which would have improved the solubility of the peptide. Thus, for this additional reason, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer and would have reasonably expected it to result in a GLP-1 analogue that is easier to formulate.

208. Second, I understand Dr. Soares is also offering an opinion that a POSA would have been motivated to use a di-AEEA spacer. I understand Dr. Soares is offering an opinion that a medicinal chemist would have reasonably expected a di-AEEA spacer to improve albumin binding. I also understand Dr. Soares agrees that a POSA would have expected the di-AEEA spacer to provide additional space between the peptide and albumin, allowing the peptide to have more room to bind to the GLP-1 receptor and induce its antidiabetic effects. Finally, given all of this, I understand Dr. Soares is offering the opinion that a medicinal chemist would have been motivated to use the di-AEEA spacer and would have expected it to extend the half-life of the peptide (via the enhanced albumin binding) and improve efficacy (via the additional space it provides).

209. Accordingly, POSAs would have been motivated to modify liraglutide with a di-AEEA spacer with a reasonable expectation of success. At the very least, using an inert linker like di-AEEA would have been a predictable use of a known option according to its known function.

(iii) A POSA would have been motivated to acylate a C₁₈ fatty diacid onto the di-AEEA spacer via a glutamic acid linker with a reasonable expectation of success

210. The last difference between semaglutide and liraglutide is the use of a C₁₈ dicarboxylic acid as opposed to a C₁₆ monocarboxylic acid at Lys²⁶. *Supra* Sections VII.C.4-5. In view of the Knudsen Patent, and a POSA's knowledge of the state of the art, a POSA would have been motivated to acylate a C₁₈ diacid onto the di-AEEA spacer via a glutamic acid linker and would have reasonably expected the resulting peptide to have a longer half-life and antidiabetic properties.

211. The Knudsen Patent disclosed various GLP-1 analogues, including liraglutide. Ex. 1012 (Knudsen Patent) at Abstract, Claims 1, 14, 187:41-188:4. According to the Knudsen Patent, the GLP-1 analogues “preferably have only one or two [lysine residues] wherein the ε-amino group of one or both [lysine residues] is substituted with a lipophilic substituent.” *Id.* at 12:23-26. The Knudsen Patent further indicated that in “a more preferred embodiment, there is only one [lysine] which is located at the carboxy terminus of the derivative of the GLP-1 analogs.” *Id.* at 12:27-29. The Knudsen Patent further disclosed that the purpose of the lipophilic substituent was “[t]o obtain a satisfactory protracted profile of action of the GLP-1 derivative.” *Id.* at 16:57-58. “[M]ost preferably,” the GLP-1 analogue contains “one lipophilic substituent.” *Id.* at 16:65-67.

212. Further, the lipophilic substituent could be an “acyl group of the formula $\text{HOOC}(\text{CH}_2)_m\text{CO—}$, wherein m is an integer from 4 to 38,” including “ $\text{HOOC}(\text{CH}_2)_{16}\text{CO—}$ ” (i.e., a C_{18} dicarboxylic acid). *Id.* at 19:17-22. As the Knudsen Patent explained, the lipophilic substituent is attached to an amino group via an acylation reaction at a carboxyl group of the lipophilic substituent, which forms a standard amide bond. *Id.* at 16:61-65. As noted above, the Knudsen Patent disclosed that “[i]n a most preferred embodiment, the lipophilic substituent is attached—optionally via a spacer—to the ϵ -amino group of a [lysine] residue contained in the parent peptide.” *Id.* at 17:55-57.

213. In addition to disclosing liraglutide as a favorable GLP-1 analogue, the Knudsen Patent disclosed other GLP-1 analogues containing various modifications. One analogue disclosed and claimed by the Knudsen Patent is $\text{Arg}^{34}\text{Lys}^{26} (\text{N}^\epsilon\text{-(}\omega\text{-carboxyheptadecanoyl)})\text{-GLP-1(7-37)-OH}$. *Id.* at 177:33-57, Claim 10. This GLP-1 analogue, like liraglutide, contained an arginine substitution at position 34 (a lysine residue in native GLP-1(7-37)) but was acylated with a C_{18} fatty diacid at the lysine residue at position 26 (i.e., Lys^{26}). According to the data in the Knudsen Patent, this GLP-1 analogue exhibited an even longer half-life than liraglutide. *Id.* at 192:30-60, Table 1 (*compare* Example 11, $\text{Arg}^{34}\text{Lys}^{26} (\text{N}^\epsilon\text{-(}\omega\text{-carboxyheptadecanoyl)})\text{-GLP-1(7-37)-OH}$, *with* Example 37, liraglutide).

TABLE 1

Test com- pound*)	Hours after sc. Administration								
	0.75	1	2	4	6	8	10	12	24
GLP-1 (7-37)		100	9	1					
Exam- ple 25	73	92	100	98	82	24	16	16	16
Exam- ple 17	76	71	91	100	84	68	30		9
Exam- ple 43		39	71	93	100	91	59	50	17
Exam- ple 37		26	38	97	100	71	81	80	45
Exam- ple 11	24	47	59	71	100	94	100		94
Exam- ple 12	36	54	65	94	80	100	85		93
Exam- ple 32	55	53	90	83	88	70	98	100	100
Exam- ple 14	18	25	32	47	98	83	97		100
Exam- ple 13	15	22	38	59	97	85	100		76
Exam- ple 38	60	53	100	66	48	39	25	29	0
Exam- ple 39	38	100	70	47	33	33	18	27	14
Exam- ple 40	47	19	50	100	51	56	34	14	0
Exam- ple 34	19	32	44	84	59	66	83	84	100

214. Accordingly, the Knudsen Patent expressly disclosed that acylating a C₁₈ fatty diacid at Lys²⁶ imparts a longer half-life to the peptide than the C₁₆ fatty acid used in liraglutide. Additionally, Knudsen 2004 reiterated that liraglutide was “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.*” Ex. 1010 (Knudsen 2004) at 3

(emphasis added). Thus, Knudsen 2004 explained that GLP-1 analogues can be prepared using fatty acids and various spacers (or linkers) with the goal of binding to albumin to extend the half-life of the peptide, just as the Knudsen Patent taught. If a POSA's goal were to make a GLP-1 analogue having a long half-life, an obvious modification to liraglutide would be to choose a fatty acid substituent having stronger noncovalent interactions with albumin than the C₁₆ monoacid used in liraglutide, particularly in view of the Knudsen Patent and Knudsen 2004

215. Accordingly, when Knudsen 2004, Dong, and Bridon are read in view of the Knudsen Patent, a POSA would have been motivated to modify liraglutide by acylating a C₁₈ fatty diacid to Lys²⁶ via a di-AEEA spacer and a glutamic acid linker in lieu of a C₁₆ fatty monoacid-glutamic acid linker group. Further, because the Knudsen Patent taught that a C₁₈ diacid results in a longer half-life without a glutamic acid linker, a POSA would have reasonably expected that including a di-AEEA spacer and glutamic acid linker would result in an even longer half-life. A POSA would expect that a fatty acid that bound albumin more tightly would work better. A POSA's knowledge of the state of the art generally would have further suggested this modification. *Supra* Section VII.C.3.b.

216. For example, as of the priority date of the '343 patent, it had long been known that C₁₈ fatty acids had stronger binding affinities for albumin than C₁₆ fatty acids. Indeed, the Cistola references disclosed that a C₁₈ fatty acid exhibited strong

binding affinities for albumin via specific interactions. *See generally* Ex. 1008 (Cistola I); Ex. 1009 (Cistola II). Importantly, the Cistola references disclosed that positively charged amino acid residues in albumin interacted with fatty acid carboxyl groups. Ex. 1008 (Cistola I) at 7; Ex. 1009 (Cistola II) at 5. Using ^{13}C NMR, Cistola I provided physicochemical information regarding the order of filling and relative occupation of individual fatty acid binding sites on albumin. Ex. 1008 (Cistola I) at 8. And both Cistola references reported that the carboxyl group of octadecanoic (or stearic) acid, which contains 18 carbon atoms, interacted with albumin via several high-affinity binding sites. Ex. 1008 (Cistola I) at Abstract; Ex. 1009 (Cistola II) at 5.

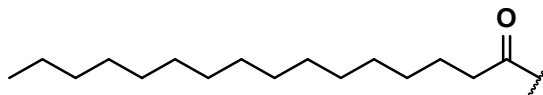
217. Similarly, Kenyon investigated the interactions of the binding of medium-chain fatty acids to human serum albumin (“HSA”) using ^{13}C NMR spectroscopy. Ex. 1032 (Kenyon) at 1. Kenyon taught that “[t]he highest affinity sites [on HSA] for both OCT [octanoic] and DEC [decanoic] have properties similar to those of binding sites for longer-chain fatty acids, such as the close proximity of the fatty acid carboxylate to basic amino acid residue(s).” *Id.* Thus, Kenyon disclosed that the carboxylate group of fatty acids bind to and interact with amino acid residues in HSA. *Id.* at Abstract, 3-4.

218. Peters, a textbook dedicated to the study of albumin, disclosed various details about albumin, including its structure and ability to interact with compounds.

Ex. 1042 (Peters) at 23-33. Peters disclosed that HSA is a protein containing 585 amino acid residues. *See, e.g., id.* at 27, 39. Peters also taught that albumin can interact with a wide spectrum of compounds, including long chain fatty acids (i.e., C₁₆-C₂₀), including various fatty acids having an 18-carbon chain. *Id.* at 93. Peters explained that long-chain fatty acids “bind in a hydrophobic pocket that is adaptable to the ligand, with its negative charge matched in a salt bond by the positive charge of a nearby lysyl or arginyl residue.” *Id.* Peters also disclosed that stearic acid exhibited stronger binding affinities for albumin than other fatty acids did. *Id.* at 99. Further, Peters taught that long-chain fatty acids were known to increase their half-life past their solubility in plasma. *Id.* at 90-93.

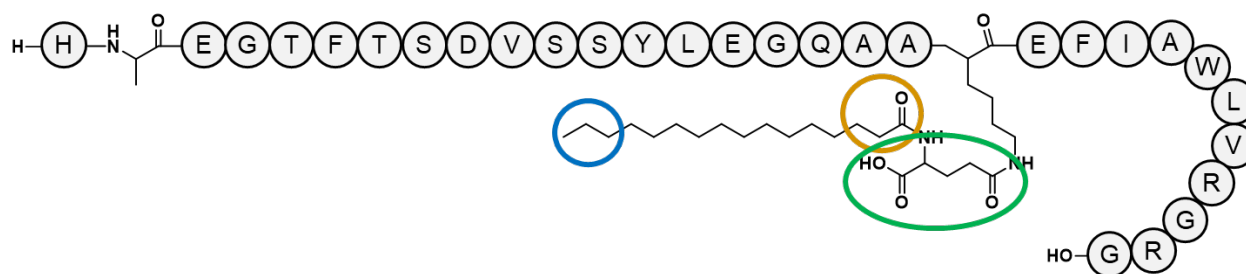
219. In my opinion, a POSA would have been motivated to modify liraglutide by replacing the C₁₆ monoacid at Lys²⁶ with a C₁₈ dicarboxylic acid at Lys²⁶. In addition, a POSA would have reasonably expected this modification to result in a GLP-1 analogue having a longer half-life than liraglutide. This is reinforced by the state of the art and general understanding of a POSA as of the priority date of the '343 patent. For instance, in view of the references discussed above, a POSA would have understood the specific non-covalent interactions by which long-chain fatty acids bind to albumin. Importantly, *all* of these references explained that it was the carboxylic acid group of the fatty acids that interacted most strongly with albumin. This is important for several reasons.

220. First, because liraglutide used a monoacid (i.e., palmitic acid, a 16-carbon fatty acid that has a carboxylate group on only one end), there was no free carboxylic acid group to interact with albumin:



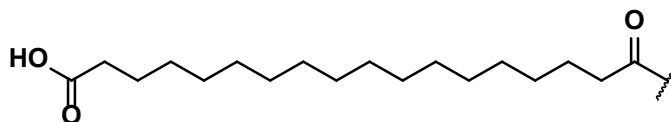
A POSA would have understood that the acylation reaction that allows the fatty acid to bind to the glutamic acid linker consumes both a carboxylic acid group, present on the fatty acid, and an amine group, present on the glutamic acid, to form a peptide bond. Thus, the carboxylic acid of palmitic acid is bound to the glutamic acid spacer and is not free to interact with albumin.

221. The following figure, which shows the structure of liraglutide, better illustrates this point:



As can be seen in this figure, the glutamic acid linker (green) bound to Lys²⁶ forms a peptide bond with the carboxylic acid group (yellow) of the palmitic acid so that the lipophilic tail of the fatty acid (blue) is left as the primary point of interaction with albumin.

222. In contrast, using a long-chain fatty *diacid* ensures that a carboxylic acid group will be free to interact with albumin. For example, the C₁₈ dicarboxylic acid disclosed in the art discussed above has the following structure:



A POSA would have readily understood that this diacid would form a peptide bond with the glutamic acid linker which would consume one of its free carboxylic acid groups, as in liraglutide above, but would leave a second carboxylic acid group free to interact with albumin. And as the prior art showed, an 18-carbon fatty acid having a free carboxylic acid group exhibited the *strongest* binding affinity to albumin of all long-chain fatty acids. *See, e.g.*, Ex. 1042 (Peters) at 99.

223. Finally, a POSA would have been motivated to retain the glutamic acid linker in liraglutide.¹³ As explained above, the thinking in the art generally was that the addition of a carboxylic acid group near a fatty acid on a peptide could enhance

¹³ As noted above, both liraglutide and semaglutide use the (S)-isomer of glutamic acid. *Supra* Sections VII.C.4-5. A POSA would be motivated to retain this isomer of glutamic acid (which, for instance, is the naturally occurring and more readily obtainable isomer) and would have no reason to contemplate using the (R)-isomer of γ -glutamic acid.

albumin binding. *See, e.g.*, Ex. 1038 (Markussen) at 7 (“Possibly, the charge mimics the carboxylate group of a fatty acid and thereby enhances binding to albumin. When the fatty acid is substituted in position Phe^{B1} there is no negative charge in the vicinity, and the binding constant becomes lower by a factor of 4.”). And the glutamic acid linker, shown in green in the figure above, increases the net negative charge. *Supra* ¶ 218.

224. Indeed, Knudsen 2000 expressly disclosed that:

Acylation with simple fatty acids increases the net negative charge of the resulting molecule by 1, whereas peptides acylated with a L-glutamoyl spacer or with diacids provide a net increase of the negative charge by 2. In the two latter cases, an enhanced effect on binding to albumin is predicted. This extra negative charge added to the acylated molecule is also expected to provide a higher solubility at physiological pH.

Ex. 1034 (Knudsen 2000) at 2. Curiously, the various Knudsen publications, which disclosed data obtained from hundreds of GLP-1 analogues, did not report any data for GLP-1 analogues derivatized with long-chain fatty diacids and glutamic acid spacers, despite their apparent understanding early on of the importance of the properties these components added to the peptide. In my opinion, this would have stuck out to a POSA as an important and unexplored series of GLP-1 analogues, the most obvious one being an analogue derivatized at Lys²⁶ with a C₁₈ diacid with a glutamic acid linker, for the reasons discussed above. Finally, a POSA would have

at least considered using a C₁₈ diacid to be predictable given the known binding function of that fatty acid to albumin. And because it was known that there was a relationship between the length and charge of a fatty acid and binding to albumin, selection of the exact length and charge would have been a matter of simply optimizing those variables.

225. Finally, I understand Dr. Soares has set forth additional reasons why a POSA would have been motivated to acylate a C₁₈ diacid to the di-AEEA spacer at Lys²⁶ via a glutamic acid linker. For those additional reasons, from the perspective of a medicinal chemist, a POSA would have been motivated to modify liraglutide in this way and would have had a reasonable expectation of success.

c. Conclusion

226. For the reasons discuss above, it is my opinion that a POSA would have identified liraglutide as a lead compound. *Supra* Section VIII.B.1.a. In addition, in view of Knudsen 2004, the Knudsen Patent, Dong, and Bridon, a POSA would have been motivated to modify liraglutide to obtain semaglutide. *Supra* Sections VIII.B.1.b. Further a POSA would have reasonably expected those modifications to result in a GLP-1 analogue with a longer half-life than liraglutide and antidiabetic properties *at least* as good as liraglutide, if not better. *Id.* In other words, a POSA would have reasonably expected these modifications to have a synergistic and cumulative effect to improve the properties of the peptide. Accordingly, in my

opinion, claims 1 and 4 of the '343 patent are unpatentable as obvious for the reasons set forth above.

2. Claims 2 and 5 of the '343 Patent

227. Claims 2 and 5 of the '343 patent recite “[a] pharmaceutical composition” that comprises the same compounds recited in claims 1 and 4, respectively, as well as a pharmaceutically acceptable excipient.” I reincorporate my analyses above to conclude that semaglutide would have been obvious. *Supra* Sections VIII.B.1.a-c.

228. Further, I note that the prior art expressly disclosed that GLP-1 peptides could be readily formulated into pharmaceutical compositions that also contained pharmaceutically acceptable excipients. *See, e.g.*, Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18; Ex. 1093 (Flink) at 3:21-24. Indeed, a POSA would have understood that for a GLP-1 analogue, or any drug for that matter, to be useful for patients (or to be tested in clinical trials), it must be formulated into a composition that also contains pharmaceutical excipients. Indeed, many excipients were well known, well catalogued, and commonly used by the priority date. Thus, as was common practice in the art generally, it is my opinion that a POSA would have been motivated to formulate semaglutide into a pharmaceutical composition with pharmaceutically acceptable excipients and would have had a reasonable expectation of success. Nothing about the structure of

semaglutide would cause a POSA to think it could not be as easily formulated into a pharmaceutical composition as liraglutide. Indeed, a POSA would expect it to be more easily formulated because of the increased hydrophilicity and negative charge from the di-AEEA linker and C₁₈ diacid moieties, which would increase solubility, as I understand Drs. Soares and Dalby have opined. For these reasons, in my opinion, claims 2 and 5 of the '343 patent are unpatentable as obvious.

3. Claims 3 and 6 of the '343 Patent

229. Claims 3 and 6 of the '343 patent recite a “method for treating type 2 diabetes in a subject” comprising administering “an effective amount” of the same compounds recited in claims 1 and 4, respectively. As noted above, I understand Dr. Bantle, Mylan’s medical expert, has opined that the medical aspects of the challenged claims would have been obvious. While I offer no opinions on those issues, I reincorporate my analyses above to conclude that semaglutide would have been obvious. *Supra* Sections VIII.B.1.a-c.

230. Further, I note that the prior art expressly disclosed that GLP-1 peptides could be used to treat type-2 diabetes in humans when administered in effective amounts. *See generally, e.g.*, Ex. 1010 (Knudsen 2004) at 3, 5; Ex. 1012 (Knudsen Patent) at 170:5-15, claim 39; Ex. 1034 (Knudsen 2000) at 2, 4. Thus, in view of the prior art, it is my opinion that a POSA would have been motivated to use semaglutide to treat hyperglycemia and/or type-2 diabetes and would have had a

reasonable expectation of success. For these reasons, in my opinion, claims 3 and 6 of the '343 patent are unpatentable as obvious.

C. Ground 2: The Challenged Claims of the '343 Patent Would Have Been Obvious Over Knudsen 2001 in View of the Knudsen Patent, Dong, and Bridon

231. In my opinion, the challenged claims of the '343 patent also would have been obvious over Knudsen 2001 in view of the Knudsen Patent, Dong, and Bridon. Thus, this combination of references relies on Knudsen 2001, whereas the combination of references discussed above relied on Knudsen 2004. Below I explain why the challenged claims would have been obvious in view of these references in the context of a “lead compound” analysis. *Supra* Section II.B. As I did above, I first explain why a POSA would have identified liraglutide as a lead compound and then explain why a POSA would have been motivated to make the chemical modifications needed to arrive at semaglutide. As above, I understand that additional experts are offering opinions on behalf of Mylan related to the medicinal chemistry, medical, and formulation aspects of the challenged claims, which are consistent with my opinions below.

1. Claims 1 and 4 of the '343 Patent

232. As explained above, for purposes of my obviousness opinions here, I address only whether semaglutide would have been obvious as of the priority date. *Supra* Sections IV; VII.D; VIII.B.1.a.

a. A POSA would have selected liraglutide as a lead compound with a reasonable expectation of success

233. I first address whether a POSA would have selected liraglutide as a lead compound. *Supra* Section VIII.B.1.a. In view of Knudsen 2001, and without the teachings of Knudsen 2004, it is my opinion that a POSA would have identified liraglutide as a lead compound.

234. First, I reiterate the general points above regarding why a POSA motivated to develop a new drug for the treatment of type-2 diabetes would have been motivated to make a GLP-1 analogue with a long half-life. *Supra* Section VIII.B.1.a. As detailed above, while a number of diabetes treatment options were available as of the priority date of the '343 patent, many of these classes of drugs had waning interest from the scientific community for various reasons (i.e., serious side effects, short durations of action, etc.) and because other more appealing options began to emerge in the 1990s and early 2000s. *Supra* Sections VII.B.1-6. Most notably, GLP-1 analogues having longer half-lives than the naturally occurring GLP-1 peptides began to emerge as promising new drug candidates for the treatment of type-2 diabetes. *Supra* Section VII.B.7. And POSAs continued to investigate whether GLP-1 analogues having longer half-lives and antidiabetic properties could be developed into a drug suitable for the treatment of type-2 diabetes requiring fewer administrations.

235. Further, as of the priority date of the '343 patent, GLP-1-based drugs were considered among the most desirable and interesting drug candidates. *Supra* Section VII.B-C. However, the naturally occurring GLP-1 peptides suffered from extremely short half-lives and it was recognized in the art that chemical modifications would be required to impart a suitable protraction profile to these peptides. *Id.* In my opinion, a POSA motivated to make a GLP-1 analogue having a long protraction profile and desirable antidiabetic properties would have identified liraglutide as a lead compound in view of the prior art.

236. Knudsen 2001 disclosed that liraglutide “was selected as *the best* compound for several reasons” and that clinical data showed liraglutide to be a promising drug candidate. Ex. 1011 (Knudsen 2001) at 5-6 (emphasis added). Indeed, Knudsen 2001 disclosed that liraglutide was one of “a series of GLP-1 derivatives designed for once-daily administration.” *Id.* at 1. According to Knudsen 2001, “the most optimal pharmacokinetic profile of a GLP-1 drug from this perspective would again be a long half-life with as few as possible peak concentrations. Thus, compounds administered several times a day have a disadvantage over compounds with only once-daily administration.” *Id.* at 3.

237. As noted above, Knudsen 2001 concluded that liraglutide (i.e., γ -L-glutamoyl(N- α -hexadecanoyl)-Lys²⁶,Arg³⁴-GLP-1(7-37)) “was selected as *the best* compound for several reasons.” *Id.* at 5 (emphasis added). First, the γ -L-Glu spacer

“gave the most potent compound.” *Id.* Second, the naturally occurring lysine residues at positions 26 and 34 “were the most preferred amino acids to derivatize because they were natural lysines and could thus be derivatized easily and without introducing any potential immunogenic changes in the amino acid sequence.” *Id.* But Knudsen 2001 further confirmed that derivatizing Lys²⁶ in particular gave the most potent and metabolically stable compound. *Id.* Thus, Knudsen 2001 explained that liraglutide was selected for clinical development. *Id.*

238. Knudsen 2001 also disclosed various clinical data that showed liraglutide to be a promising drug candidate. *Id.* at 5-6. Notably, Knudsen 2001 explained that one study “showed a more pronounced glucose lowering effect of [liraglutide] than exendin-4.” *Id.* at 6. Knudsen 2001 concluded that for a GLP-1 analogue “to be clinically useful the dynamic half-life needs to be significantly prolonged.” *Id.* And while the Knudsen team identified many highly potent GLP-1 analogues derivatized in the C-terminal part of the peptide with short and long fatty acids and amino acid-derived spacers, liraglutide in particular was identified “as a promising new treatment for type 2 diabetes.” *Id.*

239. Accordingly, in view of Knudsen 2001 alone, a POSA interested in developing a long-lasting GLP-1 analogue for the treatment of diabetes would have identified liraglutide as a lead compound. In addition, a number of additional publications available as of the priority date, which serve as exemplary references

of the background knowledge that a POSA would have had, supported the notion of using liraglutide as a lead compound. Those references and an explanation of why those references would have motivated a POSA to use liraglutide as a lead compound are set forth above. *Supra* Section VIII.B.1.a (discussing the Knudsen Patent, Knudsen 2000, Holz, and Joy). For those additional reasons, a POSA would have identified liraglutide as a lead compound.

240. As explained above, while liraglutide appeared to be a suitable candidate for the treatment of diabetes using a once-daily injection, a POSA would have been motivated to develop a GLP-1 analogue requiring less-frequent administration (i.e., having a longer half-life). *Supra* Section VIII.B.1.a. Indeed, the '343 patent acknowledged as much. *See* Ex. 1002 ('343 patent) at 1:50-53 (“[T]here is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g. once every second or third day preferably once weekly, while retaining an acceptable clinical profile.”). This would decrease the risk of patient noncompliance, and would be less burdensome in any event. And although the '343 patent purported to identify this “need,” these efforts were already underway before the priority date of the '343 patent. *See, e.g.,* Ex. 1033 (Kim) at 3-4; Ex. 1031 (Holz) at 10. Further, I understand Mylan’s medical expert, Dr. Bantle, has opined that this was the case. Finally, as explained above and reiterated below, a number of techniques and specific chemical modifications that resulted in GLP-1

peptides having longer half-lives than liraglutide, while retaining desirable therapeutic properties, were already known.

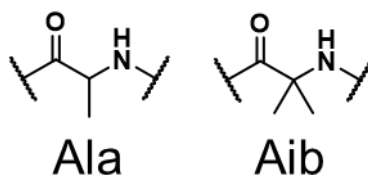
b. A POSA would have been motivated to modify liraglutide to make semaglutide with a reasonable expectation of success

241. As above, a POSA would have been motivated to make a GLP-1 analogue having a long half-life and antidiabetic properties. *Supra* Sections VII.C, VIII.B.1.a. For the reasons discussed above, a POSA would have sought to develop a GLP-1 analogue having a longer half-life than liraglutide that would require less-frequent administration. *Supra* Section VIII.B.1.b. For the reasons discussed below, a POSA would have been motivated to make the chemical modifications to liraglutide necessary to arrive at semaglutide in view of the prior art, even in the absence of Knudsen 2004. And as previously explained, the modification process would have included steps that were well known to and understood by POSAs.

(i) A POSA would have been motivated to perform an Aib⁸ substitution with a reasonable expectation of success

242. As explained above, while liraglutide contains an alanine at position 8, semaglutide has an Aib⁸ substitution. *Supra* Sections VII.C.4-5; VIII.B.1.b.i. In my opinion, for the same reasons set forth above, a POSA would have been motivated to modify liraglutide with an Aib⁸ substitution in view of Knudsen 2001, Dong, and the Knudsen Patent. *Supra* Section VIII.1.b.i. This is reinforced by a POSA's

knowledge of the state of the art, even in the absence of Knudsen 2004. *Supra* Section VIII.B.1.b.i. Further, a POSA would have reasonably expected the resulting peptide to have a longer half-life than liraglutide and antidiabetic properties. *Supra* Section VIII.1.b.i. Aib was both taught by the prior art and is structurally similar to the native Ala residue, and so would have been attractive as a very conservative substitution:



243. First, other than Knudsen 2004, the same reasons why an Aib⁸ substitution would have been obvious apply in view of Knudsen 2001, Dong, and the Knudsen Patent. *Supra* Section VIII.B.1.b.i (discussing Dong and the Knudsen Patent; explaining that Deacon, Holz, Drucker, Buckley, and Sewald demonstrate a POSA’s background knowledge and the state of the art). In addition, Knudsen 2001 would have further suggested this modification.

244. For example, Knudsen 2001 disclosed that DPP-IV metabolizes naturally occurring GLP-1 peptides at position 8. Ex. 1011 (Knudsen 2001) at 3. With this knowledge, Knudsen 2001 taught that “[a]mino acid substitutions in position 8 can give better metabolic stability against DPP-IV.” *Id.* at 5. But as Knudsen 2001 explained, the more amino acid substitutions that are performed to

the naturally occurring peptide, the greater the risk of immunogenicity problems arising. *Id.* Accordingly, when Knudsen 2001 is read in view of Dong and the Knudsen Patent (i.e., three of the references relied on in Ground 2), a POSA would have understood that an Aib⁸ substitution would have resulted in a GLP-1 peptide with a longer half-life than liraglutide and that minimizing the number of amino acid substitutions would be preferred. Thus, Dong read in view of Knudsen 2001 would have strongly suggested to a POSA that an Aib⁸ substitution would have resulted in a GLP-1 peptide with a longer half-life than liraglutide.

245. Accordingly, in my opinion, a POSA would have been motivated to modify liraglutide with an Aib⁸ amino acid substitution in view of Dong, as well as Knudsen 2001 and the Knudsen Patent, and would have reasonably expected the resulting peptide to have a longer half-life and antidiabetic properties. Further, for the same reasons explained above, this combination of references would have motivated a POSA to make only this one additional amino acid substitution to liraglutide (i.e., in addition to the Arg³⁴ substitution already present in liraglutide). *Supra* Section VIII.B.1.b.(i). This reasoning applies even in view of Knudsen 2001 instead of Knudsen 2004, because Knudsen 2001 disclosed that “[a]mino acid substitutions in position 8 can give better metabolic stability against DPP-IV” and that “any amino acid substitution poses a risk of immunogenicity.” Ex. 1011 (Knudsen 2001) at 5. Indeed, it was well understood in the art that this Aib⁸

substitution would extend the half-life of GLP-1 analogues. However, a POSA would not have stopped there, as detailed below. A POSA would have been motivated to use additional known techniques and modifications (i.e., modifications other than amino acid substitutions) to make a GLP-1 analogue having a half-life significantly longer than liraglutide.

(ii) A POSA would have been motivated to use a di-AEEA spacer with a reasonable expectation of success

246. As explained above, semaglutide contains a di-AEEA spacer between the glutamic acid linker-fatty acid moiety and Lys²⁶. *Supra* Sections VII.C.4-5; VIII.B.1.b.ii. In my opinion, for the same reasons set forth above, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer in view of Knudsen 2001, Bridon, and the Knudsen Patent, even in the absence of Knudsen 2004. *Supra* Section VIII.B.1.b.ii. Further, a POSA would have reasonably expected the resulting peptide to have a longer half-life than liraglutide with similar antidiabetic properties. *Supra* Section VIII.1.b.ii.

247. First, other than Knudsen 2004, the same reasons why a di-AEEA spacer would have been obvious apply in view of Knudsen 2001, Bridon, and the Knudsen Patent. *Supra* Section VIII.B.1.b.i (discussing Bridon and the Knudsen Patent; explaining that Kim, Sato, Sewald, and Rando demonstrate a POSA's

background knowledge and the state of the art). In addition, Knudsen 2001 would have further suggested this modification.

248. For example, Knudsen 2001 disclosed that:

Fatty acids or fatty diacids, optionally extended with a “spacer” between the epsilon-amino group of the lysine side chain and the carboxyl group of the fatty acid, were used. Acylation with simple fatty acids increases the net negative charge of the resulting molecule with one (by blocking the epsilon-amino group of the lysine), whereas peptides acylated with a L-glutamoyl-spacer or with diacids provides a further increase of the negative charge. The addition of a negative charge to the acylated molecule is expected to improve solubility at physiological pH.

Ex. 1011 (Knudsen 2001) at 3. Thus, Knudsen 2001 explained that GLP-1 analogues can be prepared using fatty acids and various spacers (or linkers) with the goal of binding to albumin to extend the half-life of the peptide, much like the technique disclosed in Bridon.

249. Further, while Knudsen 2001 disclosed that liraglutide used a glutamic acid spacer, it also acknowledged that other spacers could be used successfully. *Id.* at 4-5. Accordingly, when Knudsen 2001 is read in view of Bridon and the Knudsen Patent, a POSA would have understood that modifying liraglutide with a di-AEEA spacer at Lys²⁶ would likely result in a GLP-1 analogue having a longer half-life, particularly where an Aib⁸ substitution was made, while retaining the antidiabetic

properties of the peptide. For these additional reasons, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer at Lys²⁶ and would have had a reasonable expectation of success.

250. What's more, for the reasons discussed above, a POSA would have understood that the di-AEEA spacer would contribute additional desirable properties to the GLP-1 analogue because of its chemical nature. *Supra* Section VIII.B.1.b.ii. And as noted above, I understand Drs. Dalby and Soares have opined that a formulator and medicinal chemist likewise would have been motivated to use a di-AEEA spacer for additional reasons. *Supra* Section VIII.B.1.b.ii. Accordingly, for these additional reasons, a POSA would have been motivated to modify liraglutide with a di-AEEA spacer with a reasonable expectation of success. At the very least, using an inert linker like di-AEEA would have been a predictable use of a known linker according to its known function (i.e., linking).

(iii) A POSA would have been motivated to acylate a C₁₈ fatty diacid onto the di-AEEA spacer via a glutamic acid linker with a reasonable expectation of success

251. As explained above, semaglutide is acylated at Lys²⁶ with a C₁₈ dicarboxylic acid while liraglutide was acylated with a C₁₆ monocarboxylic acid at Lys²⁶. *Supra* Sections VII.C.4-5, VIII.B.1.b.iii. In my opinion, for the same reasons set forth above, a POSA would have been motivated to acylate a C₁₈ diacid onto the

di-AEEA spacer via a glutamic acid linker and would have reasonably expected the resulting peptide to have a longer half-life and at least similar antidiabetic properties in view of Knudsen 2001 and the Knudsen Patent, even in the absence of Knudsen 2004. *Supra* Section VIII.B.1.b.iii. Further, a POSA would have reasonably expected the resulting peptide to have a longer half-life than liraglutide and at least similar antidiabetic properties. *Supra* Section VIII.1.b.iii.

252. As discussed above, other than Knudsen 2004, the same reasons why a C₁₈ diacid and glutamic acid linker would have been obvious apply in view of Knudsen 2001 and the Knudsen Patent. *Supra* Section VIII.B.1.b.i (discussing the Knudsen Patent; explaining that Cistola I, Cistola II, Kenyon, Knudsen 2000, Markussen, and Peters demonstrate a POSA's background knowledge and the state of the art). In addition, Knudsen 2001 would have further suggested this modification.

253. For example, according to Knudsen 2001, "the most optimal pharmacokinetic profile of a GLP-1 drug from this perspective would again be a long half-life with as few as possible peak concentrations. Thus, compounds administered several times a day have a disadvantage over compounds with only once-daily administration." Ex. 1011 (Knudsen 2001) at 3. Knudsen 2001 further acknowledged that "[d]erivatizing GLP-1 with long fatty acids has been shown to

result in half-lives exceeding 10 h in healthy humans as well as type 2 diabetic patients after [subcutaneous] administration.” *Id.*

254. In particular, Knudsen 2001 explained that:

Fatty acids or fatty diacids, optionally extended with a “spacer” between the epsilon-amino group of the lysine side chain and the carboxyl group of the fatty acid, were used. Acylation with simple fatty acids increases the net negative charge of the resulting molecule with one (by blocking the epsilon-amino group of the lysine), whereas peptides acylated with a L-glutamoyl-spacer or with diacids provides a further increase of the negative charge. The addition of a negative charge to the acylated molecule is expected to improve solubility at physiological pH.

Id. But Knudsen 2001 did not report any data related to GLP-1 analogues acylated with a glutamic acid linker and *diacids*.

255. Accordingly, a POSA would have been aware that a C₁₈ diacid acylated at Lys²⁶ *without* a glutamic acid linker resulted in a peptide having a longer half-life than liraglutide, *see* Ex. 1012 (Knudsen Patent) at 192:30-60, but that *without* the glutamic acid linker, the diacid analogues appeared to lose potency, Ex. 1011 (Knudsen 2001) at 4-5. Thus, a POSA would have been motivated to combine the teachings of Knudsen 2001 and the Knudsen Patent to acylate a C₁₈ diacid via a glutamic acid linker to obtain the longer half-life and retain potency. Accordingly, in my opinion, a POSA would have been motivated to acylate a C₁₈ diacid onto the

di-AEEA spacer via a glutamic acid linker and would have reasonably expected the resulting peptide to have a longer half-life and antidiabetic properties. Finally, a POSA would have at least considered using a C₁₈ diacid to be predictable given the known binding function of that fatty acid to albumin. And because it was known that there was a relationship between the length and charge of a fatty acid and binding to albumin, selection of the exact length and charge would have been a matter of simply optimizing those variables.

256. Further, I understand Dr. Soares has set forth additional reasons why a POSA would have been motivated to acylate a C₁₈ diacid to the di-AEEA spacer at Lys²⁶ via a glutamic acid linker. For those additional reasons, from the perspective of a medicinal chemist, a POSA would have been motivated to modify liraglutide in this way and would have had a reasonable expectation of success.

c. Conclusion

257. For the reasons discuss above, it is my opinion that a POSA would have identified liraglutide as a lead compound. *Supra* Section VIII.C.1.a. In addition, in view of Knudsen 2001, the Knudsen Patent, Dong, Bridon, a POSA would have been motivated to modify liraglutide to obtain semaglutide. *Supra* Sections VIII.C.1.b. Further, a POSA would have reasonably expected those routine modifications to result in a GLP-1 analogue with a longer half-life than liraglutide and antidiabetic properties *at least* as good as liraglutide, if not better. *Id.* In other words, a POSA

would have reasonably expected these well-explored modifications to have a synergistic and cumulative effect to improve the properties of the peptide. Accordingly, in my opinion, claims 1 and 4 of the '343 patent are unpatentable as obvious for the reasons set forth above.

2. Claims 2 and 5 of the '343 Patent

258. As explained above, claims 2 and 5 of the '343 patent recite “[a] pharmaceutical composition” that comprises the same compounds recited in claims 1 and 4, respectively, as well as a pharmaceutically acceptable excipient.” I reincorporate my analyses above to conclude that semaglutide would have been obvious. *Supra* Sections VIII.C.1.a-c.

259. Further, I note that the prior art expressly disclosed that GLP-1 peptides could be readily formulated into pharmaceutical compositions that also contained pharmaceutically acceptable excipients. *See, e.g.*, Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18. Indeed, a POSA would have understood that for a GLP-1 analogue, or any drug for that matter, to be useful for patients (or to be used in clinical trials), it must be formulated into a composition that also contains pharmaceutical excipients. Thus, as was common practice in the art generally, it is my opinion that a POSA would have been motivated to formulate semaglutide into a pharmaceutical composition with pharmaceutically acceptable excipients and would have had a reasonable expectation of success. For

these reasons, in my opinion, claims 2 and 5 of the '343 patent are unpatentable as obvious

3. Claims 3 and 6 of the '343 Patent

260. Claims 3 and 6 of the '343 patent recite a “method for treating type 2 diabetes in a subject” comprising administering “an effective amount” of the same compounds recited in claims 1 and 4, respectively. As noted above, I offer no opinions on the specific medical aspects of the challenged claims, but I do reincorporate my analyses above to conclude that semaglutide would have been obvious. *Supra* Sections VIII.C.1.a-c.

261. Further, I note that the prior art expressly disclosed that GLP-1 peptides could be used to treat type-2 diabetes in humans when administered in effective amounts. *See generally, e.g.*, Ex. 1011 (Knudsen 2001) at 5-6; Ex. 1012 (Knudsen Patent) at 4:6-38, 170:5-15, claim 39; Ex. 1034 (Knudsen 2000) at 2, 4. Thus, in view of the prior art, it is my opinion that a POSA would have been motivated to use semaglutide to treat hyperglycemia and/or type-2 diabetes and would have had a reasonable expectation of success. For these reasons, in my opinion, claims 3 and 6 of the '343 patent are unpatentable as obvious.

D. Ground 3: The Challenged Claims of the '343 Patent Would Have Been Obvious in View of Common Drug Development Principles

262. Grounds 1 and 2, discussed above, included my obviousness opinions in the context of the “lead compound” obviousness test. However, as I explained above, counsel informs me that a “lead compound” obviousness analysis may not be required for the challenged claims to be found unpatentable as obvious. *Supra* Section VI. In my opinion, if the lead compound test is not required, the challenged claims would have been obvious in view of the prior art discussed above, as well as general principles used in peptide drug development as of the priority date.

263. First, for the reasons set forth above, a POSA would have understood that liraglutide was known. *Supra* Sections VII.C.4-5, VIII.B.1.a., VIII.C.1.a. Indeed, by the priority date of the '343 patent liraglutide was not only known but had been studied in detail, including through phase 2 clinical trials. *See generally*, e.g., Ex. 1010 (Knudsen 2004); Ex. 1011 (Knudsen 2001); Ex. 1034 (Knudsen 2000); Ex. 1012 (Knudsen Patent). Thus, to the extent the Board determines that liraglutide would not have been a lead compound, which it was, liraglutide was unquestionably in the prior art.

264. Second, a POSA would have been motivated to make a long-lasting GLP-1 analogue for the reasons discussed above. *Supra* Sections VII.B-C, VIII.B.1.a-b, VIII.C.1.a-b. Accordingly, a POSA would have applied techniques

used generally in the field of peptide drug development and techniques already known to be effective with respect to GLP-1 analogues.

265. Third, a POSA would have understood that the techniques used to make semaglutide were commonly employed during the peptide drug development process. *Supra* Section VII.C. This is particularly true where structure-activity-relationship information is already known, as was the case for the naturally occurring GLP-1 peptides. *See, e.g.*, Ex. 1005 (Adelhorst) at 1 (“side chains in positions 7, 10, 12, 13, and 15 are directly involved in the receptor interaction while positions 28 and 29 are important for GLP-1 to adapt the conformation recognized by the receptor”); Ex. 1010 (Knudsen 2004) at 3 (disclosing detailed SAR information); Ex. 1011 (Knudsen 2001) at 4-5 (disclosing that certain modifications were known to be effective while others negatively impacted the peptide). Further, various background references recognized that amino acid substitutions, fatty acid acylation, and the use of spacers and linkers were frequently used to generate analogues of peptides as part of the normal peptide drug development process. *See, e.g.*, Ex. 1038 (Markussen) at 7; Ex. 1045 (Sato) at 55:6-7, 130:31-33; Ex. 1067 (Sewald) at 36, 49, 179.

266. Fourth, each of the specific techniques used to make semaglutide had been applied in attempts to make GLP-1 analogues having long half-lives. For example, amino acid substitutions at position 8 specifically were an accepted means

to achieve this goal (i.e., protecting the peptide from DPP-4 degradation, thereby extending the half-life). *See, e.g.*, Ex. 1013 (Dong) at 6 (disclosing that an Aib⁸ substitution increased the half-life of GLP-1 peptides); Ex. 1010 (Knudsen 2004) at 3, Fig. 3 (disclosing that residue 8 was a site that “[m]ay be modified for DPP-IV stability”); Ex. 1011 (Knudsen 2001) at 5 (“Amino acid substitutions in position 8 can give better metabolic stability against DPP-IV”); Ex. 1012 (Knudsen Patent) at 9:40-41 (disclosing that various amino acids could be substituted at position 8); Ex. 1072 (Deacon) at 3-4 (disclosing that Aib⁸ analogues did not degrade “after 6 [hours]” but “had similar affinities compared to GLP-1 (7-36) amide”); *see also* Ex. 1031 (Holz) at 7; Ex. 1017 (Drucker 2001) at 8; Ex. 1047 (Buckley) at 25:17-30, Fig. 1. Similarly, the use of negatively charged spacers and/or linkers to modify GLP-1 analogues was a common technique used in the art. *See, e.g.*, Ex. 1014 (Bridon) at 28:56-30:67 (disclosing the modification of a GLP-1 peptide with a di-AEEA spacer); Ex. 1010 (Knudsen 2004) at 3 (“Spacers other than [glutamic acid] can be used.”); Ex. 1011 (Knudsen 2001) at 4-5 (disclosing that various spacers could be used successfully); Ex. 1034 (Knudsen 2000) at 2 (disclosing that “[a]cylation with simple fatty acids increases the net negative charge of the resulting molecule by 1, whereas peptides acylated with a L-glutamoyl spacer or with diacids provide a net increase of the negative charge by 2. In the two latter cases, an enhanced effect on binding to albumin is predicted”); Ex. 1012 (Knudsen Patent) at

17:59-60 (disclosing that several “suitable spacers,” including “succinic acid, Lys, Glu or Asp, or a dipeptide such as Gly-Lys” could be used); *see also, e.g.*, Ex. 1033 (Kim) at 3; Ex. 1045 (Sato) at 124:24-125:8, 128:5-13, 179:1-180:28.

267. Finally, the use of a C₁₈ fatty diacid was shown to increase the half-life of GLP-1 peptides. *See, e.g.*, Ex. 1012 (Knudsen Patent) at 192:30-60 (disclosing data that show a GLP-1 analogue acylated at Lys²⁶ exhibited an even longer half-life than liraglutide); Ex. 1010 (Knudsen 2004) at 3 (disclosing that fatty acid acylation was an effective method to increase the half-life of GLP-1 analogues); Ex. 1011 (Knudsen 2001) at 3 (disclosing that GLP-1 analogues acylated with fatty diacids increased the half-life and produced other benefits); *see also, e.g.*, Ex. 1008 (Cistola I) at Abstract; Ex. 1009 (Cistola II) at 5; Ex. 1032 (Kenyon) at 1, 3; Ex. 1042 (Peters) at 99.

268. Accordingly, to the extent the lead compound test is not required, it is my opinion that a POSA motivated to make a GLP-1 analogue having a long half-life and antidiabetic properties would have applied the techniques described above. And in applying those techniques, particularly in view of what was known about liraglutide and the naturally occurring GLP-1 peptides, a POSA would have inevitably ended up making semaglutide. In other words, a POSA would have been motivated to make semaglutide, even if not specifically envisioned, by applying commonly used techniques and following standard drug development procedures,

or considered it obvious to try. For this additional reason, it is my opinion that the challenged claims of the '343 patent are unpatentable as obvious.

IX. NO SECONDARY CONSIDERATIONS OVERCOME *PRIMA FACIE* OBVIOUSNESS OF THE CLAIMED SUBJECT MATTER

269. As explained above, I was informed by counsel that one of the factual inquiries relevant to an obviousness analysis is secondary considerations of non-obviousness. I understand Patent Owner must establish that these secondary considerations, or objective indicia, render claims of a patent non-obvious. I was informed that secondary considerations will only be considered if Patent Owner successfully carries its burden of establishing a “nexus” between the objective evidence and the claimed invention. I also understand that an otherwise strong showing of obviousness may stand even in the face of considerable evidence of secondary considerations.

270. In my opinion, there are no apparent secondary considerations supporting non-obviousness of the challenged claims. In addition, to the extent the Board finds that there are secondary considerations supporting non-obviousness, it is my opinion that they cannot overcome the clear showing that the challenged claims were obvious for the reasons set forth above.

271. Finally, Patent Owner has not yet presented any arguments related to secondary considerations of non-obviousness. Accordingly, I reserve the right to

address any secondary considerations put forth by Patent Owner in any later response to this declaration or Mylan's petition.

A. Semaglutide Did Not Produce Any Unexpected or Surprising Results

272. I understand one secondary consideration of non-obviousness is whether the claimed invention produced unexpected or surprising results. I understand from counsel that any evidence of unexpected results must be commensurate with the scope of the claimed invention, otherwise, it has limited probative value. I also understand from counsel that to be probative, the evidence must show that the unexpected result differs from that of the prior art. Finally, I understand from counsel that the unexpected result must be one that is different in kind and not merely in degree from the results of the prior art.

273. In my opinion, semaglutide did not produce any unexpected or surprising results. First, that semaglutide has a longer half-life than liraglutide (and other prior art GLP-1 analogues) was not surprising for the reasons discussed above. *Supra* Sections VIII.B-C. Indeed, a POSA would have expected semaglutide to have a significantly longer half-life than liraglutide in view of Knudsen 2004 or Knudsen 2001, the Knudsen Patent, Dong, Bridon, and a POSA's knowledge of the art. *Id.* These references, and the state of the art generally, suggested that an Aib⁸ substitution and acylating a C₁₈ fatty diacid at Lys²⁶ via a glutamic acid linker and a

di-AEEA spacer would result in a longer half-life via enhanced albumin binding and greater protection from DPP-4 degradation. *Id.* Accordingly, it would not have been unexpected or surprising that semaglutide could be administered less frequently than liraglutide.

274. Second, a POSA would have reasonably expected semaglutide to exhibit antidiabetic properties, as discussed above. *Supra* Sections VIII.B-C. In fact, in view of Knudsen 2004 or Knudsen 2001, the Knudsen Patent, Dong, Bridon, and a POSA's knowledge of the art, a POSA would have expected that semaglutide may exhibit increased potency and efficacy compared to liraglutide. *Id.*

275. Third, as explained above, a POSA would have expected semaglutide to be more soluble than liraglutide. *Supra* Sections VIII.B.1.b; VIII.C.1.b. In addition, I understand Dr. Soares has opined that the addition of the di-AEEA spacer would reduce the odds of aggregate formation, which would further improve the formulation and manufacturing properties. I also understand Dr. Dalby has opined that a formulator would have expected semaglutide to be easier to formulate. Thus, any formulation or manufacturing benefits attributed to semaglutide would not have been surprising or unexpected.

276. Finally, I understand semaglutide has been associated with an ability to “reduce[] body weight,” Ex. 1063 (Ozempic Label) at Section 12.2, and to “reduce the risk of major adverse cardiovascular events” in certain type-2 diabetes patients.

Id. at 1, Indications and Usage. In my opinion, a POSA would have expected semaglutide to produce these benefits, even as of the priority date of the '343 patent.

277. It was well accepted as of 2005 (and earlier) that GLP-1 analogues generally, exenatide and liraglutide specifically, helped lower body weight—a significant advantage over other classes of diabetes drugs available at the time. *Supra* Sections VII.B-C; *see also, e.g.*, Ex. 1079 (Buse) at 1; Ex. 1010 (Knudsen 2004) at 4; Ex. 1011 (Knudsen 2001) at 2, 5; Ex. 1304 (Knudsen 2000) at 1; Ex. 1055 (Madsbad) at 1. In addition, a POSA would have reasonably expected GLP-1 analogues generally, and liraglutide specifically, to produce cardiovascular benefits—another critical improvement on prior diabetes drugs. *Supra* Sections VII.B-C; *see also, e.g.*, Ex. 1010 (Knudsen 2004) at 1 (“[t]here may be specific receptors in the heart that along with the benefits of reducing blood glucose may protect from cardiovascular complications, and GLP-1 stimulates memory and learning capabilities.”), 5 (“[I]t has been suggested 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.”); Ex. 1017 (Drucker 2001) at 6. Thus, it would come as no surprise to a POSA that semaglutide also produced these effects.

B. The Prior Art Did Not Teach Away From Semaglutide

278. I understand Patent Owner may allege that the prior art “taught away” from pursuing the claimed invention. Here, Patent Owner would have to show that the prior art would have dissuaded a POSA from using liraglutide as a lead compound, or from making the modifications needed to arrive at semaglutide. For the reasons set forth above, Patent Owner will not be able to make such a showing.

279. Indeed, as explained above, Patent Owner had given to the world its playbook on how to design GLP-1 analogues having a long half-life. *See generally*, e.g., Ex. 1010 (Knudsen 2004); Ex. 1011 (Knudsen 2001); Ex. 1034 (Knudsen 2000); Ex. 1012 (Knudsen Patent). Further, others in the art had confirmed that other modifications would be expected to increase the half-life of a GLP-1 analogue while retaining or enhancing its therapeutic properties. *Supra* Sections VIII.B.1.b; VIII.C.1.b. Cumulatively, these teachings would have directed a POSA to semaglutide, not away from it. Accordingly, in my opinion, the prior art did not teach away from semaglutide.

C. There Was No Long-Felt But Unmet Need

280. I understand Patent Owner may allege that semaglutide filled a long-felt but unmet need for a diabetes treatment option. But, any long-felt but unmet need was satisfied by liraglutide well before semaglutide made it to market. Further, as explained above, a number of existing diabetes drugs existed as of the priority

date of the '343 patent that allowed patients to effectively manage type-2 diabetes. *Supra* Section VII.B. Accordingly, while semaglutide offered an improvement on the prior art treatment options, it did not fill a long-felt but unmet need.

D. There Was No Industry Skepticism

281. In my opinion, Patent Owner cannot credibly argue that there would have been industry skepticism regarding semaglutide as of the priority date of the '343 patent. As explained above, it was well accepted at the time that GLP-1 analogues were one of, if not the most, promising diabetes drugs under investigation at the time. *Supra* Section VII.C. Further, as explained above, Patent Owner had already publicly disclosed promising Phase 2 clinical trial data for liraglutide. *See, e.g.,* Ex. 1010 (Knudsen 2004) at 2-3. Finally, for the reasons set forth above, semaglutide's longer protraction profile, less-frequent administration requirements, and other properties would have been expected, not doubted. *Supra* Section IX.A.

E. Copying by Generic Drug Makers Is Irrelevant

282. I understand Patent Owner may argue that Petitioner and other generic drug companies seek to copy the invention. But I was informed by counsel that evidence of copying in the generic drug context is not probative of nonobviousness. Thus, I understand any work by Mylan or other generic drug companies to develop a semaglutide product is not evidence of nonobviousness.

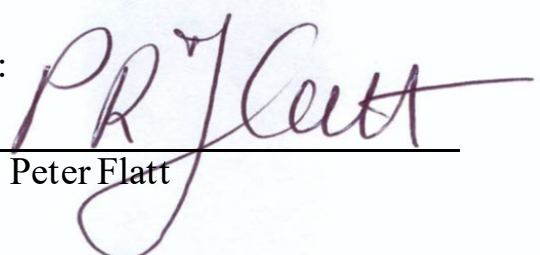
X. CONCLUSION

283. For the reasons above, it is my opinion that the challenged claims of the '343 patent are unpatentable because they would have been obvious in view of the above discussed prior art combinations.

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

Dated: March 14, 2023

By:



Dr. Peter Flatt

APPENDIX A

APPENDIX A: MATERIALS CONSIDERED

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
1005	Adelhorst, <i>Structure-Activity Studies of Glucagon-like Peptide-1*</i> , 269(9) J. BIO. CHEM. 6275 (1994)
1008	Cistola, <i>Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin I. The Filling of Individual Fatty Acid Binding Sites</i> , 262(23) J. BIO. CHEM. 10971 (1987) (“Cistola I”)
1009	Cistola, <i>Carbon 13 NMR Studies of Saturated Fatty Acids Bound to Bovine Serum Albumin II. Electrostatic Interactions in Individual Fatty Acid Binding Sites</i> , 262(23) J. BIO. CHEM. 10980 (1987) (“Cistola II”)
1010	Knudsen, <i>Glucagon-Like Peptide-1: The Basis of a New Class of Treatment for Type 2 Diabetes</i> , 47(17) J MED CHEM. 4128 (2004)
1011	Knudsen, <i>GLP-1 Derivatives as Novel Compounds for the Treatment of Type 2 Diabetes: Selection of NN2211 for Clinical Development</i> , 26(7) DRUGS OF THE FUTURE (2001)
1012	U.S. Patent No. 6,268,343 (“Knudsen Patent”)
1013	Dong, <i>Glucagon-Like Peptide-1 Analogs with Significantly Improved in vivo Activity</i> , in PEPTIDES: THE WAVE OF THE FUTURE (Michal Lebl et al. eds., 2001)
1014	U.S. Patent No. 6,514,500 (“Bridon”)

Exhibit No.	Description
1017	Drucker, <i>Development of Glucagon-Like Peptide-1-Based Pharmaceuticals Therapeutic Agents for the Treatment of Diabetes</i> , 7 CURRENT PHARM. DESIGN 1399 (2001)
1030	Holst, <i>The Incretin Approach for Diabetes Treatment Modulation of Islet Hormone Release by GLP-1 Agonism</i> , 53 (suppl. 3) DIABETES S197 (2004)
1031	Holz, <i>Glucagon-Like Peptide-1 Synthetic Analogs: New Therapeutic Agents for Use in the Treatment of Diabetes Mellitus</i> , 10(22) CURR. MED. CHEM. 2471 (2003)
1032	Kenyon, <i>¹³C NMR Studies of the Binding of Medium-Chain Fatty Acids to Human Serum Albumin</i> , 35 J. LIPID RSCH. 458 (1994)
1033	Kim, <i>Development and Characterization of a Glucagon-Like Peptide 1-Albumin Conjugate: The Ability to Activate the Glucagon-Like Peptide 1 Receptor In Vivo</i> , 52(3) DIABETES 751 (2003)
1034	Knudsen, <i>Potent Derivatives of Glucagon-Like Peptide-1 with Pharmacokinetic Properties Suitable for Once Daily Administration</i> , 43(9) J MED CHEM. 1664 (2000)
1036	LEHNINGER PRINCIPLES OF BIOCHEMISTRY (David L. Nelson et al. eds., 4th ed. 2005)
1038	Markussen, <i>Soluble, Fatty Acid Acylated Insulins Bind to Albumin and Show Protracted Action in Pigs</i> , 39(3) DIABETOLOGIA 281 (1996)
1042	Peters, ALL ABOUT ALBUMIN BIOCHEMISTRY, GENETICS, AND MEDICAL APPLICATIONS (1996)
1043	Rando, <i>Functional Incorporation of Synthetic Glycolipids into Cells</i> , 77(5) PROC. NATL. ACAD. SCI. USA 2510 (1980)
1045	WO 03/074005 ("Sato")

Exhibit No.	Description
1046	U.S. Patent No. 5,512,549
1047	WO 91/11457 (“Buckley”)
1048	Banting, <i>The Internal Secretion of the Pancreas</i> , 7 J LAB CLIN MED. 251 (1922)
1049	Bell, <i>Hamster Preproglucagon Contains the Sequence of Glucagon and Two Related Peptides</i> , 302 NATURE 716 (1983)
1051	Mojsov, <i>Insulintropin: Glucagon-like Peptide I (7-37) Co-encoded in the Glucagon Gene is a Potent Simulator of Insulin Release in the Perfused Rat Pancreas</i> , 79 J. CLIN. INVEST. 616 (1987)
1052	Ørskov, <i>Biological Effects and Metabolic Rates of Glucagonlike Peptide-1 7–36 Amide and Glucagonlike Peptide-1 7–37 in Healthy Subjects are Indistinguishable</i> , 42 Diabetes 658 (1993)
1055	Madsbad, <i>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)</i> , 27 DIABETES CARE 1335 (2004)
1063	Ozempic prescribing information (Oct. 2022)
1067	Sewald, PEPTIDES: CHEMISTRY AND BIOLOGY (2002)
1070	Luna, <i>Oral Agents in the Management of Type 2 Diabetes Mellitus</i> , 63 AM. FAM PHYSICIAN 1747 (2001)
1071	Cooper, <i>Peptides as a Platform for Targeted Therapeutics for Cancer: Peptide – Drug Conjugates (PDCs)</i> , 50 CHEM. SOC. REV. 1480 (2021)
1072	Deacon, <i>Dipeptidyl Peptidase IV Resistant Analogues of Glucagon-Like Peptide-1 which have Extended Metabolic Stability and Improved Biological Activity</i> , 41 DIABETOLOGIA 271 (1998)

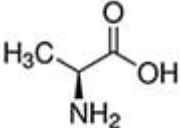
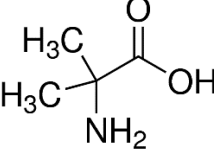
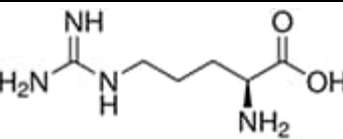
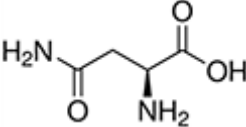
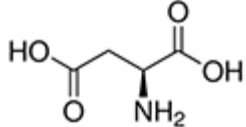
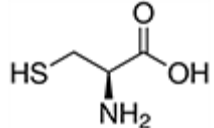
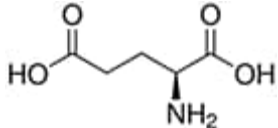
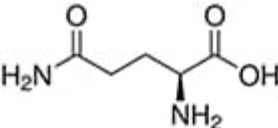
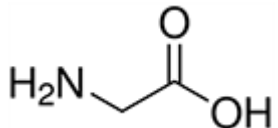
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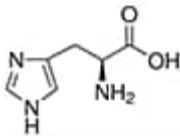
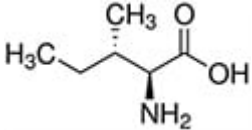
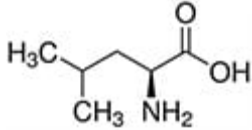
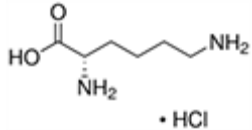
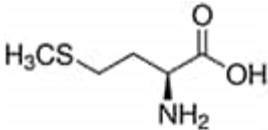
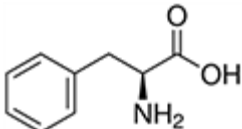
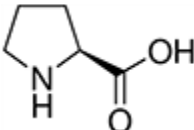
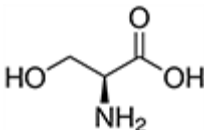
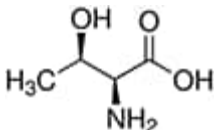
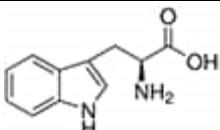
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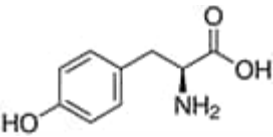
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APPENDIX B

APPENDIX B: AMINO ACID SUMMARY CHART

Amino Acid	Three-Letter Code	One-Letter Code	Chemical Structure
alanine	Ala	A	
2-amino-isobutyric acid	Aib	none	
arginine	Arg	R	
asparagine	Asn	N	
aspartic acid	Asp	D	
cysteine	Cys	C	
glutamic acid	Glu	E	
glutamine	Gln	Q	
glycine	Gly	G	

Amino Acid	Three-Letter Code	One-Letter Code	Chemical Structure
histidine	His	H	
isoleucine	Ile	I	
leucine	Leu	L	
lysine	Lys	K	
methionine	Met	M	
phenylalanine	Phe	F	
proline	Pro	P	
serine	Ser	S	
threonine	Thr	T	
tryptophan	Trp	W	

Amino Acid	Three-Letter Code	One-Letter Code	Chemical Structure
tyrosine	Tyr	Y	
valine	Val	V	