

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. IPR2023-00722

Patent No. 8,536,122

**DECLARATION OF PAUL DALBY, PH.D., IN SUPPORT OF PETITION
FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 8,536,122**

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TABLE OF ABBREVIATIONS

Full Name of Cited Reference	Abbreviation
U.S. Patent No. 8,536,122	'122 patent
U.S. Patent No. 7,022,674	'674 patent
Boylan, <i>Parenteral Products</i> , in MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)	Boylan
U.S. Patent No. 6,514,500	Bridon
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)	Dong
WO 03/002136	Flink
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
U.S. Patent No. 6,268,343	Knudsen Patent
Rando, <i>Functional Incorporation of Synthetic Glycolipids into Cells</i> , 77(5) PROC. NATL. ACAD. SCI. USA 2510 (1980)	Rando
REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)	Remington
WO 00/37098	WO098

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

I. QUALIFICATIONS AND BACKGROUND

A. Education and Experience; Prior Testimony

2. I earned my doctorate at Cambridge University, UK, in 1998 where I studied protein folding mechanisms, using protein engineering to alter the relative stabilities of the native, denatured, intermediate and transition states, and evaluating the effects of a range of temperature, pH and presence of viscosity modifiers in the formulation. From 1998 to 2000, I was a postdoctoral fellow at the University of Pennsylvania, where I studied the relationship between protein structure, stability, and function through protein engineering and biophysical characterization, and also methods to improve stability and minimize aggregation in protein therapeutic formulations. In 2000, I was appointed Lecturer at University College London

(UCL) in the Department of Biochemical Engineering. My research focused on new strategies for evolutionary protein and enzyme design, researching factors to strengthen protein stability during biopharmaceutical downstream processes, and developing stability analysis methods to optimize the process and maintain proper protein formulation.

3. From 2004-2006, I was principal investigator on a project funded by the Department of Trade and Industry in conjunction with the Health Protection Agency, UK, to establish protein, process, and formulation engineering methods for novel protein fusions. During that time, I was an active member of the Protein Society, the Royal Society of Chemistry, the RSC Biotechnology Group Committee, the Institution of Chemical Engineers, and the American Chemical Society. I organized conferences on behalf of these organizations including the 2006 “Therapeutic Proteins: Chemical & Enzymatic Modification” in London. Based on my work with the previous organizations, I was invited to a joint BIA & Bioprocess UK workshop in 2005. The workshop led to the establishment of biopharmaceutical formulation as a funding priority in the DTI technology transfer program.

4. In 2006, I began a long-term collaboration with the National Institute of Biological Standards and Controls in the UK to improve the tools and techniques used in liquid and freeze-dried protein formulation development. The projects undertaken used biophysical analysis and statistical design of experiments

approaches, to optimize formulations, and to characterize and understand the impact of different excipients on their properties.

5. In 2007, I was appointed Senior Lecturer at UCL and in 2009 I was appointed Reader at UCL in the Department of Biochemical Engineering. From 2011 until 2016, I was Co-Director of the Engineering and Physical Sciences Research Council (EPSRC) Centre for Innovative Manufacturing at UCL.

6. I am currently Co-Director of the EPSRC Future Targeted Healthcare Manufacturing Hub and Director of the EPSRC Doctoral Training Centre for Innovative Manufacturing at UCL. In 2013, I was appointed Professor at UCL, Department of Biochemical Engineering, and in 2016 was named Deputy Head, Department of Biochemical Engineering (Research) at UCL. Over the course of my career at UCL, I have supervised numerous projects resulting in novel research and development in the field of protein stability. These projects resulted in developing a novel method for measuring protein stability in microtiter plates; development of enhanced bioprocessing for advanced pharmaceutical proteins, using directed evolution; and new methods of protein engineering and formulation resulting in improved biopharmaceutical stability. The various projects are listed in my CV. I have presented the results of my research on protein therapeutics and formulation at numerous international conferences including the Protein Science Forum 2005, the Cambridge Healthtech Institute 2006,ACHEMA 2006, BioProcess International

2007, 2011 & 2012, Recovery XIV 2010, World Biopharm Forum 2011, and the Royal Society of Chemistry MiBIO 2012.

7. I am considered a key influencer of research priorities in the UK in the area of biopharmaceutical formulation. I have been appointed to lead government and industry groups for establishment of biopharmaceutical formulation protocols. I have provided consultancy services to a number of companies, including: Ajinomoto, Angel Biotechnology, Cambridge Antibody Technology (now MedImmune and owned by AstraZeneca), and Clear Capital Ltd. I also serve on the Scientific Advisory Board for Leukocare GmbH in Germany, and UMabs in the USA and China, and have presented my work at international conferences on biopharmaceutical formulation development.

8. I have been given numerous research grants to research and supervise projects impacting the biochemical protein industry. My research interests include: accelerating therapeutic protein and vaccine formulation design for stability in both liquid and lyophilized forms; biophysical characterization of protein aggregation and stability in formulations and bioprocess manufacturing; protein engineering for stability; using directed evolution, structural analysis, bioinformatics and computational design, high-throughput bioprocess design, including precipitation and inclusion body refolding; design and development of novel analytical methods for bioprocess monitoring and characterization of formulations.

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

- *Celltrion, Inc. v. Genentech, Inc.*, IPR2022-00578, -579 (PTAB);
- *XOMA (US) LLC v. MorphoSys AG*, Case No. 01-21-0004-4508 (ICDR, Nov. 2022);
- *Novo Nordisk Inc. v. Mylan Institutional LLC*, C.A. No. 1:19-cv-01551-KAJ-SRF (D. Del.); and
- *Merck & Co Inc. v. Wyeth*, NSD1381/2017 (Australia).

10. My qualifications are further described on my *curriculum vitae*, which can be found at Exhibit 1025.

B. Basis for Opinions and Materials Considered

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

C. Retention and Compensation

12. Mylan retained me as a technical expert to provide various opinions about the '122 patent. I am being compensated at a rate of 360 GBP per hour plus expenses for this work. My compensation is in no way tied to the outcome of this proceeding or to the content of this declaration, and it has not altered my opinions.

II. LEGAL STANDARDS

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

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

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

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

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).

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

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

III. PERSON OF ORDINARY SKILL IN THE ART

18. In my opinion, the following definition of a POSA applies to the claims of the '122 patent. I reserve the right to amend and/or supplement my opinions on unpatentability if a different definition of a POSA is adopted or agreed to.

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

20. In my opinion, the following definition of a POSA applies to the claims of the '122 patent. The subject matter of the claims of the '122 patent falls within the medicinal, chemical, and pharmacological arts and encompasses the skills, education, and expertise of a team of individuals working together to develop and formulate GLP-1 analogues, as well as to use the GLP-1 analogues to treat patients having type-2 diabetes or related conditions. Such a team would have included individuals with an M.D., Pharm.D., or doctoral degree(s) in chemistry, biochemistry, 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.

21. Alternatively, the POSA would (1) 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.

22. 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.

23. With respect to claim 13 of the '122 patent, the team would have included an individual with a PhD 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.

24. As explained above, and as is evident from my CV, I met the qualifications of a POSA as of the priority date of the '122 patent. Within this definition, my background focuses on the formulation aspects of the claims of the '122 patent.

IV. THE '122 PATENT [EX. 1001]

25. I have read the '122 patent, including its claims, which is titled "Acylated GLP-1 Compounds." I understand that the '122 patent has 16 issued claims, of which only claim 1 is an independent claim. The '122 patent lists Jesper Lau, Florencio Zaragoza Doerwald, Paw Bloch, and Thomas Kruse Hansen as inventors.

26. The '122 patent was filed on March 5, 2012, as U.S. Patent Application No. 13/412,283, a continuation of application No. 11/908,834, filed as application No. PCT/EP2006/060855, filed on March 20, 2006, and now U.S. Patent No. 8,129,343. The '122 patent also 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.

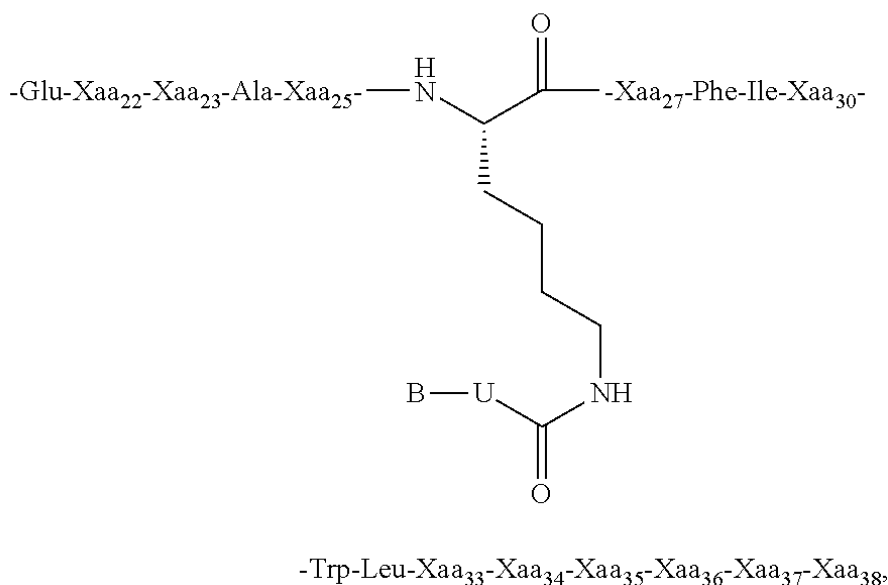
27. I understand the earliest priority date to which the challenged claims of the '122 patent are entitled is March 18, 2005, the filing date of European application No. 05102171. Therefore, references that pre-date March 18, 2005, are prior art to the '122 patent. To the extent Patent Owner later asserts and/or proves that the

challenged claims are entitled to an earlier priority or invention date, I reserve the right to supplement this declaration.

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

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

Xaa₇-Xaa₈-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Xaa₁₆-Ser-Xaa₁₈-Xaa₁₉Xaa₂₀-



wherein

Xaa₇ is L-histidine, D-histidine, desamino-histidine, 2-amino-histidine, β -hydroxy-histidine, homohistidine, N ^{α} -acetyl-histidine, α -fluoromethyl-histidine, α -methyl-histidine, 3-pyridylalanine, 2-pyridylalanine, or 4-pyridylalanine;

Xaa₈ is Gly, Val, Leu, Ile, Lys, Aib, (1-aminocyclopropyl) carboxylic acid, (1-aminocyclobutyl) carboxylic

acid, (1-aminocyclopentyl) carboxylic acid, (1-aminocyclohexyl) carboxylic acid, (1-aminocycloheptyl) carboxylic acid, or (1-aminocyclooctyl) carboxylic acid;

Xaa₁₆ is Val or Leu;

Xaa₁₈ is Ser, Lys, or Arg;

Xaa₁₉ is Tyr or Gln;

Xaa₂₀ is Leu or Met;

Xaa₂₂ is Gly, Glu, or Aib;

Xaa₂₃ is Gln, Glu, Lys, or Arg;

Xaa₂₅ is Ala or Val;

Xaa₂₇ is Glu or Leu;

Xaa₃₀ is Ala, Glu, or Arg²;

Xaa₃₃ is Val or Lys;

Xaa₃₄ is Lys, Glu, Asn, or Arg;

² I understand that while claim 1 originally recited “Xaa₃₃ is Ala, Glu, or Arg,” a certificate of correction was issued by the USPTO on April 4, 2015, to revise this claim term to read “Xaa₃₀ is Ala, Glu, or Arg.”

Xaa₃₅ is Gly or Aib;

Xaa₃₆ is Arg, Gly, Lys, or is absent;

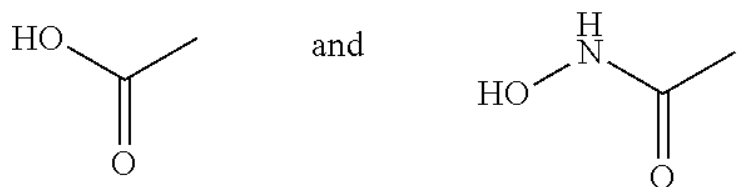
Xaa₃₇ is Gly, Ala, Glu, Pro, Lys, or is absent;

Xaa₃₈ is Lys, Ser, amide, or is absent;

and where U is a spacer selected from [various spacers];

and

where B is an acidic group selected from



29. Dependent claim 13 recites:

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

V. CLAIM CONSTRUCTION

30. 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.

31. No terms relevant to my opinions require construction beyond the plain and ordinary meaning.

VI. SUMMARY OF OPINIONS

32. As explained above, my background is related to the development of pharmaceutical formulations. Thus, my opinions focus on pharmaceutical formulation aspects of the challenged claims.

33. I understand Mylan's expert, Dr. Peter Flatt, is offering opinions from the perspective of a POSA with a background focused on chemical, biological, and/or biochemical aspects of the claims of the '122 patent. In particular, I understand Dr. Flatt has offered opinions that the compound known as semaglutide, which I understand Dr. Flatt explains is encompassed by claim 1 of the '122 patent, would have been obvious (i.e., a POSA would have been motivated to make semaglutide). Thus, I rely on Dr. Flatt's opinions to conclude that semaglutide would have been obvious.

34. I also understand Mylan has retained Dr. Christopher Soares, who opines from the perspective of a medicinal chemist, and Dr. John Bantle, who opines from the perspective of a medical doctor. As discussed above, my opinions are from

the perspective of a formulator who would collaborate with other POSAs like Drs. Flatt, Soares, and Bantle.

35. First, while I offer no opinions on whether a POSA would have been motivated to make the compound semaglutide, I offer limited opinions in support of Dr. Flatt with respect to certain chemical modifications required to make semaglutide. *Infra* Section IX.A.

36. Second, claim 13 of the '122 patent is directed to a pharmaceutical composition comprising the compound of claim 1 (i.e., semaglutide) and a pharmaceutically acceptable excipient. *Supra* Section IV. In my opinion, formulating semaglutide and a pharmaceutically acceptable excipient into a pharmaceutical composition required no more than standard knowledge and routine skill. Indeed, as discussed in detail below, the prior art disclosed that many GLP-1 analogues, including a first-generation GLP-1 analogue known as liraglutide, had been formulated into pharmaceutical compositions that contained 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. In addition, a POSA would have had a reasonable expectation of success in doing so in light of the prior art and/or the knowledge and skill of a POSA.

VII. BACKGROUND ON GLP-1 COMPOUND FORMULATIONS

A. Pharmaceutical formulations generally

37. Well before the priority date of the '122 patent, POSAs regularly formulated drug substances, including therapeutic peptides, into pharmaceutical compositions. Indeed, commercially available drug products rarely, if ever, contain a drug substance on its own. Rather, drug substances must be formulated into suitable pharmaceutical compositions that contain additional inactive ingredients, or excipients, for administration to patients. *See generally, e.g.*, Ex. 1088 (Remington); Ex. 1089 (Boylan). By the priority date of the '122 patent, a vast number of excipients were commonly used to formulate drug substances. *See, e.g.*, Ex. 1088 (Remington) at 41; Ex. 1089 (Boylan) at 18-24. Further, pharmaceutical compositions could be made using commonly employed techniques that were well understood by POSAs. *See, e.g.*, Ex. 1088 (Remington) at 37-38; Ex. 1089 (Boylan) at 18-19.

38. As just one example, therapeutic peptides were regularly formulated in parenteral formulations. *See, e.g.*, Ex. 1089 (Boylan) at 35-36. Parenteral formulations can be administered through intravenous, subcutaneous, intradermal, intramuscular, intraarticular, and intrathecal injection. *See, e.g.*, Ex. 1089 (Boylan) at 8-9 (Table 1). And POSAs were well aware of specific excipients that were commonly used to make suitable parenteral formulations of therapeutic peptides.

See, e.g., Ex. 1088 (Remington) at 41; Ex. 1089 (Boylan) at 18-24. Those are just examples, of course. The point is that there were a range of excipients that were in standard use in pharmaceutical compositions that had known purposes.

39. Further, POSAs recognized the importance of maintaining the physical and chemical stability of a drug formulation to minimize the risk of impurities during manufacturing, storage, and handling. *See, e.g.*, Ex. 1088 (Remington) at 28-29, 37-38; Ex. 1089 (Boylan) at 7-8, 39. Indeed, because excipients can have profound effects on the performance of a drug, POSAs understood that it was important that parenteral preparations be “of the very best quality and provide the maximum safety for the patient.” Ex. 1088 (Remington) at 37. Further, regulatory agencies like FDA require the role and amount of each excipient to be justified, require the developer to ensure there are no incompatibilities between the excipients and the active drug, and require ongoing quality control of each excipient during manufacturing. *See, e.g.*, Ex. 1089 (Boylan) at 47. Accordingly, the role of excipients in pharmaceutical formulations was well understood industry-wide.

B. GLP-1 compounds were well known

40. Before the priority date of the '122 patent, POSAs were aware of the two different truncated forms of naturally occurring glucagon-like peptide-1 (GLP-1): GLP-1(7-36) and GLP-1(1-37). Ex. 1012 (Knudsen Patent) at 4:48-60. GLP-1(7-37) has the following sequence where X is Gly:

7 8 9 10 11 12 13 14 15 16 17
His-Ala-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Val-Ser-
18 19 20 21 22 23 24 25 26 27 28
Ser-Tyr-Leu-Glu-Gly-Gln-Ala-Ala-Lys-Glu-Phe-
29 30 31 32 33 34 35 36
Ile-Ala-Trp-Leu-Val-Lys-Gly-Arg-X

Id. The prior art explained that these naturally occurring peptides showed great promise for their antidiabetic effect, and so scientists sought to use these peptides as therapeutic agents. *See, e.g.*, Ex. 1010 (Knudsen 2004) at 1; Ex. 1011 (Knudsen 2001) at 1-2.

41. The prior art also taught that chemically modified versions of these naturally occurring peptides (i.e., analogues) had been made and were advancing in clinical trials. *See generally, e.g.*, Ex. 1010 (Knudsen 2004); Ex. 1011 (Knudsen 2001). As these analogues were being developed, so too were pharmaceutical formulations suitable to deliver the analogues to patients. *See, e.g.*, Ex. 1093 (Flink) at Abstract; Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18. Thus, many formulations of GLP-1 analogues were described in the art by the priority date of the '122 patent. *See, e.g.*, Ex. 1093 (Flink) at 37:25-46:5; Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18.

42. As discussed above, before the priority date of the '122 patent, POSAs were provided with substantial guidance to prepare formulations of peptides generally. *Supra* Section VII.A. To no surprise, POSAs utilized this guidance to make GLP-1 formulations, including, for example, parenteral formulations that included various well-known excipients such as buffers, preservatives, isotonic agents, and vehicles. *See, e.g.*, Ex. 1093 (Flink) at 37:25-46:5; Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18. The prior art also taught that GLP-1 compounds could be formulated into injectable formulations. Ex. 1012 (Knudsen Patent) at 216:15-57.

43. However, it was also well known that GLP-1 compounds had problems with solubility and stability. *See, e.g.*, Ex. 1092 (WO098) at 3-4; Ex. 1093 (Flink) at 3:21-24. Therefore, POSAs sought to optimize GLP-1 compounds, and formulations that could alleviate these issues, to provide more soluble and stable formulations. *See, e.g.*, Ex. 1012 (Knudsen Patent) at 5:13-15; Ex. 1092 (WO098) at 7 (“In order to overcome the problems of chemical and physical stability of GLP-1 formulations, the present inventors have developed a shelf-stable formulation of GLP-1.”); Ex. 1091 ('674 patent) at 5:39-43 (“The discoveries described . . . have been combined to provide novel preparations of polypeptide compositions for parenteral administration comprising glycerin that have improved chemical stability compared to polypeptide compositions previously known.”).

C. Liraglutide and formulations of liraglutide were well known

44. As discussed above, before the priority date of the '122 patent, GLP-1 analogues and related formulations were well known in the art. *Supra* Section VII.B. Indeed, the '122 patent identifies examples of suitable GLP-1 analogues. Ex. 1001 ('122 patent) at 1:23-43 (citing WO 96/29342; WO 98/08871; WO 99/43708; WO 00/34331; WO 00/69911; WO 02/46227). These references likewise disclosed pharmaceutical formulations containing the GLP-1 analogues that are physically and chemically stable at high concentrations, which are suitable for subcutaneous injection. *See, e.g.*, Ex. 1093 (Flink) at 4:17-30.

45. One GLP-1 analogue that was well-published in the art before the priority date of the '122 patent was Novo Nordisk's liraglutide (also called NN2211). *See, e.g.*, Ex. 1010 (Knudsen 2004) at 1; Ex. 1011 (Knudsen 2001) at 1-2. And like other GLP-1 analogues under investigation, pharmaceutical formulations of liraglutide had been developed and disclosed. Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18.

VIII. SCOPE AND CONTENT OF THE PRIOR ART

46. I identify below the prior art references supporting my expert opinions on unpatentability of claim 13 of the '122 patent, including references rendering the claim obvious. All the references I cite in this document would have been known and publicly available to a POSA as of the relevant priority date.

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

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

A. Knudsen 2004 [Ex. 1010]

49. 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 '122 patent under at least 35 U.S.C. § 102(a) because it was published before the earliest priority date of the '122 patent.

50. Knudsen 2004 disclosed benefits of 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). 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.* at 3.

51. Knudsen 2004 also disclosed that 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.*

B. Knudsen 2001 [Ex. 1011]

52. 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.

53. 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.” *Id.* at 3. Therefore, “compounds administered several times a day

have a disadvantage” over compounds with less-frequent administration. *Id.* 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.*

54. Knudsen 2001 explained that “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.*

C. The Knudsen Patent [Ex. 1012]

55. U.S. Patent No. 6,268,343 (“Knudsen Patent”) is titled “Derivatives of GLP-1 Analogs” and issued July 31, 2001, from U.S. Patent Application No. 09/258,750, filed on February 26, 1999. Novo Nordisk A/S is listed as the assignee of Knudsen. Ex. 1012 (Knudsen Patent) at (73).

56. The Knudsen Patent disclosed “GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making an [sic] using same.” *Id.* at Abstract. The Knudsen Patent stated “[i]t is a further object of the invention to provide a pharmaceutical composition with improved solubility and stability.” *Id.* at 5:13-15.

57. The Knudsen Patent taught that “[p]referably, the pharmaceutical compositions comprise an isotonic agent, a preservative and a buffer. Examples of

isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol. Suitable buffers include sodium acetate and sodium phosphate.” *Id.* at 168:1-6.

58. The Knudsen Patent disclosed “pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g. as described in Remington’s *Pharmaceutical Sciences*, 1985 or in Re[m]ington: *The Science and Practice of Pharmacy*, 19th edition, 1995.” *Id.* at 169:24-28. The Knudsen Patent also disclosed that, “[f]or example, injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.” *Id.* at 169:29-33.

59. The Knudsen Patent also taught “[i]n a preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection.” *Id.* at 169:38-40. “Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, e.g. a lyophilised product, which has to be dissolved in a solvent before it can be injected.” *Id.* at 169:40-44.

D. Dong [Ex. 1013]

60. Exhibit 1013 (“Dong”) is an article by Jesse Z. Dong et al. titled “Glucagon-Like Peptide-1 Analogs with Significantly Improved *in vivo* Activity.” It was published in 2001.

61. Dong stated that GLP-1’s “effectiveness in type 2 diabetes patients has been demonstrated in clinical evaluations,” but its use “as a therapeutic agent is greatly hampered by its short plasma half-life.” Ex. 1013 (Dong) at 6. Dong also disclosed the use of an “aminoisobutyric acid” moiety at position 8 of GLP-1. *Id.*

E. Bridon [Ex. 1014]

62. Exhibit 1014 (“Bridon”) is U.S. Patent No. 6,514,500, which is titled “Long Lasting Synthetic Glucagon Like Peptide [GLP-1]” and issued February 4, 2003. Ex. 1014 (Bridon) at 1. It described “modified peptides [to be] administered to treat humans with diabetes.” *Id.* at Abstract.

63. Bridon discussed creating GLP-1 analogues “with long duration of action for the treatment of diabetes.” *Id.* at 1:10-15. As part of its discussion of GLP-1 analogues, Bridon disclosed that “[l]inking groups”—otherwise known as spacers—could be used to “link or connect reactive groups” to GLP-1. *Id.* at 3:10-20. Bridon disclosed that among the known linking groups was [2-(2-amino)ethoxy]ethoxy acetic acid (“AEEA”), *id.* at 3:19-20, and disclosed numerous examples of GLP-1 analogues that utilized two AEEA groups (i.e., a di-AEEA

spacer) attached to the Lys residues in GLP-1. *See, e.g., id.* at 2:4-13, 28:56-30:67 (Example 5), 31:45-32:22 (Example 7).

F. Other art that informs the POSA's knowledge

1. WO 03/002136 ("Flink") [Ex. 1093]

64. Flink is titled "Stable Formulation of Modified GLP-1," and was filed on June 27, 2002, and published on January 9, 2003. Flink claims priority to six Danish applications filed between June 28, 2001, and January 18, 2002. Ex. 1093 (Flink) at (30). Novo Nordisk A/S is listed as an Applicant. *Id.* at (71). The named inventors are James M. Flink, Silke Møller Larsen, Simon Bjerregaard Jensen and Dorthe Kot Engelund. *Id.* at (72).

65. Flink described pharmaceutical formulations containing GLP-1 compounds that are physically and chemically stable at high concentrations, which are suitable for subcutaneous injection. *Id.* at 4:17-30. Flink incorporated by reference multiple patent applications providing examples of suitable GLP-1 compounds. *See, e.g., id.* at 24:10-12 (citing WO 98/08871, WO 99/43705, WO 99/43706, WO 99/43707, WO 99/43708, WO 99/43341).

66. Flink explained that unlike small molecules, "proteins are sensitive to both chemical and physical degradation." *Id.* at 3:14-15. Flink stated that "GLP-1 is known to be prone to instability due to aggregation" and that both chemical and

physical “degradation pathways may ultimately lead to loss of biological activity of the protein drug.” *Id.* at 3:18-20.

67. Flink disclosed pharmaceutical formulations that may include “a GLP-1 compound, and a buffer,” wherein said formulation has a pH from 7.0 to 10.” *Id.* at 4:32–5:14. Flink taught that the buffer may be selected from “sodium acetate, sodium carbonate, citrate, glycylglycine, histidine, glycine, lysine, arginin [sic], sodium dihydrogen phosphate, disodium hydrogen phosphate, sodium phosphate, [or] tris(hydroxymethyl)-aminomethan.” *Id.* at 18:27-30. Flink further described “glycylglycine, sodium dihydrogen phosphate, disodium hydrogen phosphate, and sodium phosphate” as “preferred.” *Id.* at 18:30-33.

2. *Remington [Ex. 1088]*

68. Remington is titled *Remington: The Science and Practice of Pharmacy* and was published in 2000. I understand that Remington is prior art to the ’122 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest possible priority date.

69. Remington provided guidance to POSAs seeking to develop various types of pharmaceutical formulations, including parenteral formulations, solid orally available dosage forms, and others. *See generally* Ex. 1088 (Remington). Remington disclosed that various types of excipients, including vehicles, antimicrobial agents, buffers, antioxidants, tonicity agents, and others, were commonly used in making

parenteral formulations. *Id.* at 41. Remington also disclosed various techniques and methods for preparing parenteral formulations. *Id.* at 37-38.

3. *Boylan [Ex. 1089]*

70. Boylan is titled “Parenteral Products” and was published as a chapter in the textbook *Modern Pharmaceutics* in 1996. I understand that Boylan is prior art to the ’122 patent under at least 35 U.S.C. § 102(b) because it was published more than one year before the earliest possible priority date.

71. Boylan provided POSAs with general guidance on the formulation of parenteral products. Ex. 1089 (Boylan) at 7-53. Boylan disclosed that various commonly used excipients could be used to make a parenteral formulation. *Id.* at 18-19 (Table 2). Boylan also disclosed information pertinent to the formulation of proteins and peptides specifically. *Id.* at 35-36.

4. *Additional prior art and references*

72. In addition to the references discussed above and throughout this declaration, I utilize the knowledge and expertise of a POSA. Also, in this declaration I cite to references in addition to those recited and summarized above, including to provide background on the state of the art at the priority date. All references, whether summarized above or not, that were publicly available prior to the priority date of the ’122 patent are within the scope of the prior art.

IX. UNPATENTABILITY OF THE CLAIMS OF THE '122 PATENT

73. As noted above, I understand that Dr. Flatt has opined that the challenged claims of the '122 patent would have been obvious over the following combinations of prior art references (i.e., grounds):

Ground 1: Knudsen 2004 in view of the
Knudsen Patent, Dong, and Bridon.

Ground 2: Knudsen 2001 in view of the Knudsen
Patent, Dong, and Bridon.

Ground 3: The Prior Art in view of Common Drug Development
Principles.

I also understand that Dr. Soares has opined that certain aspects of the challenged claims would have been obvious. I understand that both Dr. Flatt and Dr. Soares have opined that the semaglutide compound itself would have been obvious as a pharmaceutical compound of interest.

74. As detailed below, it is my opinion that a POSA would have been motivated to use the di-AEEA linker in a GLP-1 analogue, and particularly when modifying liraglutide, with a reasonable expectation of success based on certain formulation considerations. It is also my opinion that claim 13 of the '122 patent would have been obvious over any of Grounds 1-3.

- A. A POSA would have been motivated for formulation reasons to modify liraglutide with a di-AEEA spacer and a C₁₈ diacid, and would have reasonably expected it to result in a GLP-1 analogue that is easier to formulate**

75. I understand that Dr. Flatt, as to Grounds 1-3, has explained why a POSA would have identified liraglutide as a lead compound and explained why a POSA would have been motivated to make the chemical modifications needed to arrive at semaglutide. I also understand that Dr. Flatt and Dr. Soares have both offered opinions on this point.

76. I further understand that the chemical modifications described by Dr. Flatt and Dr. Soares, and for which they each offered the opinion that the modifications would have been obvious, are:

- Replacing the alanine residue at position 8 in liraglutide with an aminoisobutyric acid residue;
- Adding a “di-AEEA” spacer between the lysine residue at position 26 and the glutamic acid-fatty acid substituent; and
- Replacing liraglutide’s C₁₆ fatty acid substituent with a C₁₈ fatty diacid substituent.

77. As noted, one of these modifications would have entailed use of a “di-AEEA” spacer. Another modification involved replacing liraglutide’s C₁₆ fatty acid substituent with a C₁₈ fatty diacid substituent. In my opinion, a POSA in the field of

formulations would have been motivated to make these modifications to liraglutide and would have reasonably expected it to result in a GLP-1 analogue that is easier to formulate. Indeed, chemically modifying a compound of interest to improve its properties for purposes of formulation was a common strategy. *See, e.g.*, Ex. 1089 (Boylan) at 16-17 (“Improvement of the properties of a drug may be achieved by the chemical modification of the parent drug. The preparation of an ester, salt, or employed other modification of the parent structure may be employed with parenteral drugs to increase stability, alter drug solubility, enhance depot action, ease formulation difficulties, and possibly, decrease pain on injection”).

78. I understand that Dr. Flatt has opined that a POSA interested in developing a long-lasting GLP-1 analogue would have identified liraglutide as a lead compound for numerous reasons. As explained above, however, a POSA would have recognized that liraglutide could suffer from some formulation-related issues that would guide structural modifications.

79. Indeed, GLP-1 analogues in general were known in the art to suffer from instability, poor solubility, and aggregation. *Supra* Section VII.B; *see also* Ex. 1093 (Flink) at 3:21-24; Ex. 1092 (WO098) at 3-4; Ex. 1012 (Knudsen Patent) at 222:19-44, Fig. 1; Ex. 1034 (Knudsen 2000) at 1. A POSA would have recognized that solubility would clearly be a challenge given how hydrophobic liraglutide is, particularly because of the presence of the C₁₆ monoacid (i.e., a lipophilic moiety).

This was confirmed by Knudsen 2000 and the Knudsen Patent, which explained that liraglutide suffered from aggregation issues. Ex. 1012 (Knudsen Patent) at 222:19-44, Fig. 1; Ex. 1034 (Knudsen 2000) at 1. Thus, from a pharmaceutical-formulation standpoint, it is my opinion that a POSA would have been motivated to modify liraglutide to make a GLP-1 analogue likely to have increased water solubility. 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 stay in solution for the duration of the manufacturing process. As detailed below, 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.

80. First, with respect to the C₁₈ diacid modification, it is my opinion that this change would have improved the solubility of the peptide relative to liraglutide. This is so at least because the long lipophilic tail from the C₁₆ moiety is swapped for a long-chain fatty acid with a negatively charged, water-loving carboxylate group. As Knudsen 2001 acknowledged, a POSA would have understood that the addition of a negative charge would improve the solubility of the resulting analogue. Ex. 1011 (Knudsen 2001) at 3. Thus, in my opinion, a formulator would have been motivated to make the C₁₈ diacid modification and would have reasonably expected it to improve the solubility of the peptide.

81. Second, it is my understanding that Drs. Flatt and Soares explained that liraglutide and similar analogues in the art contained a spacer (also called a linker) that physically separated the albumin-binding fatty acid moiety from the GLP-1 peptide backbone responsible for its biological activity. In my opinion, the choice of the chemical structure of that spacer would have been guided in part by formulation considerations.

82. I understand that Dr. Soares has explained that there would have been different general chemical categories of spacers, including polyethylene glycol (PEG), alkyl, peptide, and ester spacers, and that categories of linkers other than PEG-based linkers would have suffered from instability or hydrophobicity (solubility problems). I agree. These concerns would have led a POSA away from using those categories of linkers.

83. In my experience, PEG-based linkers were commonly and conveniently used in peptides, and they were (and are) frequently used to provide water solubility, reduce toxicity, and provide a molecule with lower immunogenicity. For at least these reasons, PEG-based linkers would be preferred over other categories from a formulation perspective.

84. I understand that Dr. Soares and Dr. Flatt explained that the prior art identified a subset of PEG-based linkers—the di-AEEA linker—as one that had been preferred and advantageously used with therapeutic peptides, and with GLP-1

analogues in particular. To these opinions, I add that a POSA with a background in formulations also would have been motivated to use the di-AEEA spacer for formulation reasons.

85. The di-AEEA spacer is polar and facilitates hydrogen bonding, which a POSA would have known would make the peptide analogue more soluble. *See, e.g.*, Ex. 1043 (Rando) at 1. Additionally, adding the spacer to the existing liraglutide analogue, rather than merely replacing the glutamyl linker with the spacer, would maintain the negative charge of the analogue, making the analogue easier to dissolve, as acknowledge by Knudsen 2001. Ex. 1011 (Knudsen 2001) at 3. The di-AEEA spacer would also increase the molecule's hydrophilicity and maintain its negative charge, increasing polarity relative to liraglutide and thereby increasing its solubility. *See, e.g.*, Ex. 1043 (Rando) at 1 (describing the AEEA moiety as "a hydrophilic spacer group"). I also note that a more soluble compound has the advantage that it could be formulated under a wider range of excipients and pH conditions, and it would be less prone to solubility issues or precipitation. *See, e.g.*, Ex. 1089 (Boylan) at 16-17. It would also make the peptide easier to formulate from a manufacturing standpoint, regardless of which dosage form (i.e., solid, parenteral, etc.) was ultimately used. *See, e.g.*, Ex. 1089 (Boylan) at 24, 35.

86. Because of the known problems with liraglutide that I addressed above, a POSA therefore would have been motivated to use a di-AEEA spacer and a C₁₈

fatty diacid together because the POSA would have reasonably expected it to make the peptide easier to formulate. A formulator would have been motivated to implement a di-AEEA spacer between the fatty acid and existing glutamic acid linker because they would have expected that the di-AEEA spacer-diacid combination would have the benefit of making the GLP-1 analogue more hydrophilic, which a POSA would have expected to improve the solubility of the peptide while maintaining its ease of formulation and manufacture.

87. Thus, for this additional reason, a POSA would have been further motivated to modify liraglutide with a di-AEEA spacer between the peptide backbone and the fatty diacid with the existing glutamic acid linker, and would have reasonably expected it to result in a GLP-1 analogue that is easier to formulate.

B. A POSA would have been motivated to formulate a modified liraglutide into a pharmaceutical composition with a “pharmaceutically acceptable excipient” with a reasonable expectation of success

88. Claim 13 of the '122 patent recites a “pharmaceutical composition” comprising the compound from claim 1 (which I understand to include semaglutide) and “a pharmaceutically acceptable excipient.” Ex. 1001 at 131:16-18.

89. I understand that Dr. Flatt has opined that developing semaglutide (i.e., the compound) would have been obvious, and that Dr. Soares has also opined that aspects of semaglutide’s structure would have been obvious. Additionally, I

explained above, *see supra* ¶¶ 75-87, why a POSA would be motivated for formulation reasons to include certain aspects of semaglutide's structure.

90. If semaglutide would have been an obvious compound for pharmaceutical investigation or use, then the remaining aspects of claim 13 would also have been obvious. In short, pharmaceutical compositions require excipients, and the use of excipients is well understood.

91. The prior art of any of Grounds 1-3 would have motivated a POSA to formulate a pharmaceutical composition with a pharmaceutically acceptable excipient. The Knudsen Patent disclosed that GLP-1 analogues could be readily formulated into pharmaceutical compositions containing pharmaceutically acceptable excipients—such as “an isotonic agent, a preservative and a buffer.” *Supra* ¶ 57 (citing Ex. 1012 (Knudsen Patent) at 168:1-6). The Knudsen Patent gives numerous other examples of using excipients with GLP-1 analogues, including liraglutide. Ex. 1012 (Knudsen Patent) at 4:36-38, 167:63-168:8, 169:54-57, 170:5-10, 216:17-222:18.

92. The Knudsen Patent also explained that “conventional techniques” could be used to prepare pharmaceutical compositions of GLP-1 analogues. *See supra* ¶ 58. Finally, the Knudsen Patent taught that GLP-1 analogues could be formulated into lyophilised or dissolved compositions. *See supra* ¶ 59.

93. Further, the Knudsen Patent disclosed “GLP-1 derivatives having a lipophilic substituent, pharmaceutical compositions comprising same, and methods of making an [sic] using same.” Ex. 1012 (Knudsen Patent) at Abstract. The Knudsen Patent stated “[i]t is a further object of the invention to provide a pharmaceutical composition with improved solubility and stability.” *Id.* at 5:13-15.

94. The Knudsen Patent taught that “[p]referably, the pharmaceutical compositions comprise an isotonic agent, a preservative and a buffer. Examples of isotonic agents are sodium chloride, mannitol and glycerol. Examples of preservatives are phenol, m-cresol, methyl p-hydroxybenzoate and benzyl alcohol. Suitable buffers include sodium acetate and sodium phosphate.” *Id.* at 168:1-6. Accordingly, the prior art gave guidance of specific excipients that could be used with a reasonable expectation of success.

95. The Knudsen Patent disclosed that “pharmaceutical compositions of the present invention may be prepared by conventional techniques, e.g. as described in Remington’s *Pharmaceutical Sciences*, 1985 or in Re[m]ington: *The Science and Practice of Pharmacy*, 19th edition, 1995.” *Id.* at 169:24-28. The Knudsen Patent also disclosed “[f]or example, injectable compositions of the GLP-1 derivative of the invention can be prepared using the conventional techniques of the pharmaceutical industry which involves dissolving and mixing the ingredients as appropriate to give the desired end product.” *Id.* at 169:29:33.

96. The Knudsen Patent also taught “[i]n a preferred embodiment of the present invention, the GLP-1 derivative is provided in the form of a composition suitable for administration by injection.” *Id.* at 169:38-40. “Such a composition can either be an injectable solution ready for use or it can be an amount of a solid composition, e.g. a lyophilised product, which has to be dissolved in a solvent before it can be injected.” *Id.* at 169:40-44.

97. Further, as explained above, a compound to be used in either animal testing, clinical testing, or treatment of humans must be formulated, and formulations always contain excipients. *Supra* Section VII.A. The Knudsen Patent itself called this “conventional.” *See supra* ¶ 58. A POSA would have been well aware of what excipients are “pharmaceutically acceptable” because there is a wealth of literature on that topic, including references such as *Remington’s Pharmaceutical Sciences* and the *Handbook of Pharmaceutical Excipients*, which are common reference texts.

98. A POSA would even believe semaglutide to be more appropriate than liraglutide for formulation, owing to its greater hydrophilicity and charge, which would have improved solubility. *See supra* Section IX.A.

99. In my opinion, a POSA would have had a motivation to formulate a GLP-1 compound (here, semaglutide) into a “pharmaceutical composition” containing a “pharmaceutically acceptable excipient,” recited in claim 13 with a

reasonable expectation of success. Thus, the subject matter of claim 13 of the '122 patent would have been obvious to a POSA over any of Grounds 1-3.

C. No secondary considerations overcome prima facie obviousness

1. The formulations recited in the '122 patent produce no unexpected results

100. I understand that, to show unexpected results, Patent Owner must prove that the alleged invention produced benefits that were unexpected over the closest prior art. Patent Owner might assert that the claimed formulations showed unexpected results. In my opinion, the subject matter of the claims of the '122 patent formulations were disclosed, contemplated, and/or claimed in the prior art. *See, e.g.,* Section IX.A–B. The '122 patent presents no unexpected results from those formulations.

101. For all of the reasons explained herein, a POSA as of the priority date of the '122 patent would have expected to formulate the claimed semaglutide compound with “a pharmaceutically acceptable excipient.” The prior art disclosed semaglutide formulations with preferred excipients. A POSA would have had a reasonable expectation of success of making such a formulation using conventional techniques of the pharmaceutical industry as taught in the prior art. *See* Ex. 1093 (Flink); Ex. 1012 (Knudsen Patent).

102. Further, a POSA would have expected semaglutide to be more soluble than liraglutide. *Supra* Section IX.A–B. A formulator therefore 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.

2. *There was no long-felt but unmet need for the formulations recited in the '122 patent*

103. I understand that, to show long-felt but unmet need, Patent Owner must prove that the art long suffered from a problem to which the alleged invention offered a solution. To the extent Patent Owner asserts that the formulations claimed in the '122 patent satisfied a long-felt but unmet need, any need for such a formulation would have been met by formulations disclosed in the prior art.

104. As explained above, a number of existing diabetes drugs existed as of the priority date of the '122 patent that allowed patients to effectively manage type-2 diabetes. Therefore, any long-felt but unmet need Patent Owner may allege was satisfied by the formulations disclosed in the prior art.

3. *There was no praise of the formulations recited in the '122 patent*

105. To the extent Patent Owner asserts that there is any evidence of praise in the industry for the formulations claimed in the '122 patent, I disagree. I am not aware of any praise by others in the field for the formulation aspects of the '122 patent (*i.e.*, semaglutide with “a pharmaceutically acceptable excipient”).

106. As explained above, the claimed formulation was expressly disclosed and/or contemplated by the prior art (for example, Flink, the Knudsen Patent, the '674 patent, and WO098), so any praise in the industry would not be a result of the formulation elements in the '122 patent.

4. *There was no industry skepticism of the formulations recited in the '122 patent*

107. To the extent Patent Owner asserts that there is any evidence of industry skepticism that the formulations claimed in the '122 patent would work, I disagree. The claimed formulation was expressly disclosed and/or contemplated by the prior art (for example, Flink, the Knudsen Patent, the '674 patent, and WO098), so any skepticism would have to be directed to the specific results of using the formulation, which are inherent. Thus, even if Patent Owners could show that others considered alternative formulations to be superior to the GLP-1 agonist formulations disclosed in the prior art, it would not change the fact that the formulation was known in the prior art.

X. RESERVATION OF RIGHTS

108. I reserve the right to supplement and/or expand on the opinions I have set forth in this declaration based on the information I have reviewed and/or based on any additional information produced in discovery, modifications of the Board's

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

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

Dated: March 14, 2023

By:

A handwritten signature in black ink, appearing to read "PDalby", written over a horizontal line.

Dr. Paul Dalby

EXHIBIT A

EXHIBIT A

Exhibit No.	Description
1001	U.S. Patent No. 8,536,122
1002	U.S. Patent No. 8,129,343
1003	Prosecution history excerpts for U.S. Patent No. 8,536,122
1004	Prosecution history excerpts for U.S. Patent No. 8,129,343
1010	Knudsen, <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”)
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)
1043	Rando, <i>Functional Incorporation of Synthetic Glycolipids into Cells</i> , 77(5) PROC. NATL. ACAD. SCI. USA 2510 (1980)
1088	REMINGTON: THE SCIENCE AND PRACTICE OF PHARMACY (Alfonso R. Gennaro ed., 20th ed. 2000)
1089	Boylan, <i>Parenteral Products</i> , in MODERN PHARMACEUTICS (Gilbert S. Banker et al. eds., 3d ed. 1996)
1091	U.S. Patent No. 7,022,674

Exhibit No.	Description
1092	WO 00/37098
1093	WO 03/002136 (“Flink”)