

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BPI LABS, LLC,
Petitioner,

v.

ELI LILLY & CO.,
Patent Owner.

IPR2025-01346
Patent No. 9,474,780

DECLARATION OF ZHAOHUI SUNNY ZHOU, PH.D.

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I, Zhaohui Sunny Zhou, Ph.D., declare as follows:

I. QUALIFICATIONS

1. I am a Professor in the Department of Chemistry and Chemical Biology at Northeastern University, Boston, MA. I am also a Faculty Fellow of the Barnett Institute for Chemical and Biological Analysis. I am an Advisor and coordinator with the Industry PhD program for full-time employees. I hold a position as Affiliated Faculty with the Bioengineering and Biology departments at Northeastern University. I have held faculty appointments from 2000 to the present. My research over the last 34 years has involved pioneering work in the areas of polypeptides and proteins. This research involved peptide and protein chemistry, analysis, engineering, and therapeutic development, and includes extensive work on peptide drugs including GIP and GLP-1 receptor agonists. In particular, I have worked directly on GLP-1 receptor agonists, such as exenatide (e.g., its conjugation and engineering).

2. I graduated from Peking University, Beijing, China, earning a B.S. in Organic Chemistry in 1990. In my undergraduate studies, I worked in the laboratory of Professor Quing-Zhong Zhou in the Department of Chemistry, and my research was focused on polymer chemistry and phase transfer catalysis. Subsequently, from 1990-1991, I worked as a scientist and research associate for Dr. Qi-Pin Gao in the Department of Medicinal Chemistry and Formulation,

Academy of Traditional Chinese Medicine & Materia Medica, Changchun, Jilin, China. My work as a research assistant focused on natural product isolation, analysis and derivatization, e.g., polysaccharide (carbohydrate)-drug conjugates; and drug formulation.

3. I subsequently earned a Ph.D. in Bioorganic Chemistry in 1997 from The Department of Chemistry and Molecular Biology, The Skaggs Institute of Chemical Biology, The Scripps Research Institute, La Jolla, California. I obtained my Ph.D. under Professor Donald Hilvert (currently at the Federal Institute of Technology (ETH) Zurich, Honggerberg, Switzerland). My Ph.D. research focused on catalytic antibodies for pericyclic reactions, cofactor-dependent oxidations and reductions, medium effects in enzyme catalysis, and artificial enzymes for peptide and protein synthesis.

4. From 1997-2000, I was a Research Fellow in the laboratory of Professor Rowena G. Matthews at the University of Michigan, Ann Arbor, Michigan. My research efforts were focused on biochemical and biophysical studies of metallo-enzymes. From 2000-2006 I was an Associate Professor with tenure (2006) and Assistant Professor in the Department of Chemistry, Associate Member, School of Molecular Biosciences; Graduate Faculty, Program in Pharmacology and Toxicology; Faculty of the NIH Biotechnology Training

Program on Protein Chemistry, Washington State University, Pullman, Washington.

5. In 2007 I began my current role as a Professor in the Department of Chemistry and Chemical Biology at Northeastern University, Boston, MA. From 2019-2021, I also worked as a Visiting Professor in Dermatology at Massachusetts General Hospital (MGH), and a Visiting Scientist at the Wellman Center for Photomedicine, Harvard Medical School, Boston, MA, working with Professor Tayyaba Hasan.

6. Currently, my laboratory (aka “SunnyLand”) applies protein chemistry, analysis and engineering to biology and medicine. One program is “Hybrid Modality Engineering of Proteins” – a platform to introduce non-canonical chemical moieties and/or scaffolds into peptides and proteins to confer novel functions (modes of action) otherwise unavailable via recombinant technology. One application is the conditional release and activation of therapeutics (i.e., prodrugs), such as by light (photomedicine). The second is to devise chemo-enzymatic methodologies to characterize protein post-translational modifications (PTMs), such as crosslinking, isoaspartic acid formation (asparagine deamidation), S-adenosyl-methionine (AdoMet or SAM)-dependent methylations, as well as, unknown PTMs and analytical artifacts. In my research efforts with my laboratory, I often collaborate with biologists and clinicians alike, investigating the

biological effects and critical attributes of protein pharmaceuticals. Over the past two decades, I have been actively collaborating with and consulting for more than 20 biopharma companies, including Abbott/AbbVie, Amgen, Takeda and Dragonfly. Since 2020, I have been a co-founder and advisor of NIRa Biosciences (now a subsidiary of Alys Pharmaceuticals) with the support of venture capital (VC) fund. The work at NIRa centers on antibody-drug conjugate (ADC) that can be activated by light. The new platform for photoimmunotherapy is deployed toward immuno-dermatology and immuno-oncology, providing spatially defined, cell-targeted therapy.

7. I have over 70 research publications and my work has been published in numerous journals well-known within the field of polypeptide and protein synthesis. I have been named as an inventor on 12 patents and applications, all in the field of polypeptides and chemical synthesis and proteins, including their synthesis, design and therapeutic applications.

8. For a more detailed listing of my credentials and Publications, please see my curriculum vitae.¹

II. SCOPE OF WORK

9. I am informed that BPI Labs, LLC (“BPI”) is filing a petition with the United States Patent and Trademark Office for *Inter Partes* Review of U.S. Patent

¹ EX1003, *Curriculum Vitae* of Zhaohui Sunny Zhou, Ph.D.

No. 9,474,780 to Bokvist et al. (EX1001, “Bokvist et al.,” the “challenged patent,” “the ’780 Patent”). Polsinelli retained me on behalf of BPI as a technical expert in this matter to provide expert opinions regarding the ’780 Patent.

10. My opinions are based on my specialized education, training, knowledge, skills, training, and experience in peptide chemistry as well as on the materials cited in this declaration. For convenience, a full listing of the documents cited in this declaration, including the citation for each reference, is provided in the Appendix at the end of my declaration. I reserve the opportunity to address any additional facts, documents, or arguments subsequently presented.

11. BPI is compensating me at the rate of \$600 per hour for services. No part of my compensation is dependent on my opinions or the outcome of this proceeding. I have no financial interest in the outcome of this matter.

III. LEGAL STANDARDS

12. I have a general understanding of validity based on my experience with patents and my discussions with counsel.

13. I have a general understanding of prior art and priority dates based on my experience with patents and my discussions with counsel.

14. I have been advised that the burden in this proceeding is on BPI to demonstrate the unpatentability of the challenged claims.

15. I understand that a patent claim is invalid under 35 U.S.C. § 103 as being obvious only if the differences between the claimed invention and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person of ordinary skill in that art. An obviousness analysis requires consideration of four factors: (1) scope and content of the prior art relied upon to challenge patentability; (2) differences between the prior art and the claimed invention; (3) the level of ordinary skill in the art at the time of the invention; and (4) the objective evidence of non-obviousness, such as commercial success, unexpected results, the failure of others to achieve the results of the invention, a long-felt need which the invention fills, copying of the invention by competitors, praise for the invention, skepticism for the invention, or independent development.

16. I understand that a prior art reference is proper to use in an obviousness determination if the prior art reference is analogous art to the claimed invention. I understand that a prior art reference is analogous art if at least one of the following two considerations is met. First a prior art reference is analogous art if it is from the same field of endeavor as the claimed invention, even if the prior art reference addresses a different problem and/or arrives at a different solution. Second, a prior art reference is analogous art if the prior art reference is reasonably

pertinent to the problem faced by the inventor, even if it is not in the same field of endeavor as the claimed invention.

17. I further understand that the law recognizes several specific guidelines that inform the obviousness analysis. First, I understand that a reconstructive hindsight approach to this analysis, i.e., the improper use of post-invention information to help perform the selection and combination, or the improper use of the listing of elements in a claim as a blueprint to identify selected portions of different prior art references in an attempt to show that the claim is obvious, is not permitted. Second, I understand that any prior art that specifically teaches away from the claimed subject matter, i.e., prior art that would lead a person of ordinary skill in the art to a specifically different solution than the claimed invention, points to non-obviousness, and conversely, that any prior art that contains any teaching, suggestion, or motivation to modify or combine such prior art reference(s) points to the obviousness of such a modification or combination. Third, I understand that if a claimed invention that arises from the modification or combination of one or more prior art references uses known methods or techniques that yield predictable results, then that factor also points to obviousness. Fourth, I understand that if a claimed invention that arises from the modification or combination of one or more prior art references is the result of known work in one field prompting variations of it for use in the same field or a different one based on design incentives or other

market forces that yields predictable variations, then that factor also points to obviousness. Sixth, I understand that if a claimed invention that arises from the modification or combination of one or more prior art references is the result of a substitution of one known prior art element for another known prior art element to yield predictable results, then that factor also points to obviousness.

18. I further understand that it must be shown that one having ordinary skill in the art at the time of the invention would have had a reasonable expectation that a modification or combination of one or more prior art references would have succeeded.

19. In relation to the obviousness of molecular compounds, it has been explained to me that a “lead compound” analysis may be utilized for determining the obviousness of chemical compounds. This analysis first involves determining whether a person of ordinary skill would have selected the prior art compound(s) as lead compounds, or starting points, for further development efforts. It is my understanding that a “lead compound” is a compound in the prior art that would be promising to modify in order to improve its properties. It has been explained to me that a lead compound may be considered a natural choice for further development efforts. In determining whether a person of ordinary skill would have selected a prior art compound as a lead, it is my understanding that the analysis is guided by evidence of the compound’s pertinent properties, which may include positive

attributes such as activity and potency, as well adverse effects such as toxicity, or other adverse effects/properties.

20. I also understand that the obviousness of a chemical compound may be based on a “lead compound” that a POSA would view as promising to modify in order to improve upon its properties and activities, and subsequently obtaining a compound with better properties and activities. The presence of promising and useful properties and activities in a lead compound can serve as motivation for a person of ordinary skill to make structurally similar compounds (e.g., derivatives). Moreover, I understand that the lead compound need not be a single compound, but can be one of a group of promising compounds. It has been explained to me that, when the claimed compound and prior art compounds possess a sufficiently close structural relationship, it can create an expectation in light of the totality of the prior art, that the new compound will have similar activities and properties to the old compound. The new compounds need not be expected to be superior to (or even as desirable as) the prior art compounds for the structurally similar compounds to be *prima facie* obvious.

21. I understand that compounds which are position isomers (i.e., structures that have the same molecular formula, but differ only in the position of a functional group on the same parent base structure) or homologs generally are of sufficiently close structural similarity that there is a presumed expectation that such

compounds possess similar properties. Homology and isomerism involving close structural similarity must be considered with other relevant facts. The prior art compounds need not be true homologs or isomers of the claimed compounds to render the claimed compounds obvious when the similarity between the chemical structures and properties is sufficiently close that one of ordinary skill in the art would have been motivated to make the claimed compounds. Accordingly, the question of obviousness based on structural similarity to a prior art compound focuses on whether the state of the art was sufficient for a POSA to infer that the structural differences between the claimed compound and the prior art compound would preserve sufficient utility of the compound sufficient to warrant making the new compound.

22. I am informed that the patent owner, Eli Lilly & Co. (“Lilly”), bears the burden to produce evidence of secondary considerations indicating non-obviousness. It has also been explained to me that a finding of surprising or unexpected results may be established if the data demonstrates a difference in kind (i.e., a fundamentally new or different result or property), and not merely a difference in degree.

IV. OVERVIEW OF THE '780 PATENT

23. The '780 Patent is entitled "GIP and GLP-1 Co-Agonist Compounds."² The '780 Patent is generally directed to "dual incretin peptide mimetic compounds that agonize receptors for both human glucose-dependent insulintropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1), and may be useful for treating type 2 diabetes mellitus (T2D)."³ Both GIP and GLP-1 are natural incretins (i.e., they stimulate insulin secretion) that are critical for glucose homeostasis.⁴ Physiologically, GIP and GLP-1 are secreted from the gut following a meal, and enhance insulin secretion, nutrient disposal, and sensation of satiety.⁵ The '780 Patent admits that their stimulation of insulin secretion was known to reduce blood glucose levels and protect pancreatic beta cells.⁶ It also states that GLP-1 was known to inhibit glucagon secretion, gastric emptying and food intake, which leads to weight loss.⁷

24. The patent admits that use of these prior art incretins individually was known, but asserts that existing incretin treatments were limited in several respects. The '780 Patent admits that dosing of GLP-1 analogues has been found to be limited by adverse effects, such as nausea, vomiting, and elevated corticosterone

² EX1001 ('780 Patent), title.

³ EX1001 ('780 Patent), 1:1-8.

⁴ EX1001 ('780 Patent), 1:28-31.

⁵ EX1001 ('780 Patent), 1:20-36.

⁶ EX1001 ('780 Patent), 1:21-28.

⁷ EX1001 ('780 Patent), 1:25-28.

levels, often preventing dosing from reaching full efficacy for glycemic control and weight loss.⁸ The '780 Patent also acknowledges the understanding in the art that native GIP and GLP-1 are inactivated rapidly by the ubiquitous DPP-IV protease, making them useful only for short-term metabolic control.⁹

25. The '780 Patent also explains that GIP analogues with GIP/GLP-1 co-agonist activity were known in the art, and even cites to WO 2013/164483 to Just et al., WO 2014/192284 to Asami et al., and WO 2011/119657 to Alsina-Fernandez et al., as examples of previous applications that disclosed co-agonist compounds.¹⁰ Additionally, the '780 Patent explains that it was known in the art that certain structural modifications of GIP and GLP-1 agonists were known to have specific effects on the properties and functions of the compounds. The '780 Patent acknowledges that it was known that the use of fatty acid side chains as albumin binding motifs improve the pharmacokinetics of GIP and GLP-1 peptides by extending the half-life of the compound.¹¹ While not expressly stated, the understanding that fatty acids bind to albumin in the blood, thereby extending the half-life of the compound, was expressly discussed in one of the patent

⁸ EX1001 ('780 Patent), 1:36-40, 2:13-22.

⁹ EX1001 ('780 Patent), 1:41-44.

¹⁰ EX1001 ('780 Patent), 1:55-57.

¹¹ EX1001 ('780 Patent), 2:4-6.

applications cited by the '780 Patent as previously disclosing co-agonists of GIP and GLP-1 (i.e., WO 2013/164483 to Just et al.).¹²

26. Despite the previous disclosure of co-agonists of GIP and GLP-1, the '780 Patent asserts that a need still existed for a “balanced” co-agonism of GIP and GLP-1 receptors that could provide weight loss, have stability against deactivation by DPP-IV (while not inducing immunogenicity), and support once-weekly dosing.¹³ The patent describes “balanced” activity as an affinity for GLP-1/GIP receptors in an *in vitro* binding assay at a molar ratio that is close to 1:1, including 1:1, 2:1, 3:2, 1:2, or 2:3.¹⁴

27. The '780 Patent presents “an embodiment of the present invention” in the form of “a compound of Formula I,” illustrated below:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS ;

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO—(CH₂)_b—CO₂H wherein a is 1 to 2 and b is 10 to 20; X₃ is Phe or 1-Nal; and the C-terminal amino acid is optionally amidated as a C-terminal primary

¹² See EX1008 (Just), 49:3 to 50:2 (“it is thought that the lipophilic substituent binds albumin in the blood stream, thus shielding the compounds employed in the context of the invention from enzymatic degradation which can enhance the half-life of the compounds”); 50:24-31 (“[t]he lipophilic substituent may include a hydrocarbon chain having 10 to 24 carbon (C) atoms...it can include a functional group in the end of the lipophilic chain, e.g., carboxylic acid which may or may not be protected during synthesis.”).

¹³ EX1001 ('780 Patent), 2:28-41, 1:45-54.

¹⁴ EX1001 ('780 Patent), 6:36-43.

amide (SEQ ID NO: 11), or a pharmaceutically acceptable salt thereof.¹⁵

When X₁ is Aib, X₂ is Aib, and X₃ is Phe (F), the compound of Formula I has the following base structure (the same base structure present in tirzepatide), which is consistent with SEQ ID Nos. 3 and 11 provided in the '780 Patent:

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-K-A-F-V-Q-W-L-I-A-G-G-P-S-S-G-A-P-P-P-S						
5	10	15	20	25	30	35

28. I note that the '780 Patent acknowledges that the “compounds of the present invention may be prepared by a variety of procedures known in the art,” and that the “reagents and starting materials are readily available to one of ordinary skill in the art.”¹⁶ The '780 Patent further acknowledges that pharmaceutical compositions for administering the resulting peptides “are well known in the art.”¹⁷ I agree that preparing and formulating the peptides using methods known in the art was well within the skill of a POSA prior to the filing of the '780 Patent in 2015.

A. Claims of the '780 Patent

¹⁵ EX1001 ('780 Patent), 2:53-65.

¹⁶ EX1001 ('780 Patent), 8:44-54, *see also Id.*, 9:40-10:55, 11:51-56, 12:53-55, 13:3-5, 13:24-26, 13:45-47, 13:65-67, 14:15-17 (peptides generated using routine prior art solid-phase peptide synthesis).

¹⁷ EX1001 ('780 Patent), 7:45-64 (citing *Remington's Pharmaceutical Sciences*, 21st ed., Lippincott, Williams & Wilkins, 2006) and others).

29. The '780 Patent lists 18 claims.¹⁸ I understand that the claims define what the inventors allege to be the invention. Claim 1 is broadly directed to a genus of compounds as shown below:

1. A compound of Formula:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS;

wherein

X₁ is Aib;

X₂ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO—(CH₂)_b—CO₂H wherein a is 1 to 2 and b is 10 to 20;

X₃ is Phe or 1-Nal;

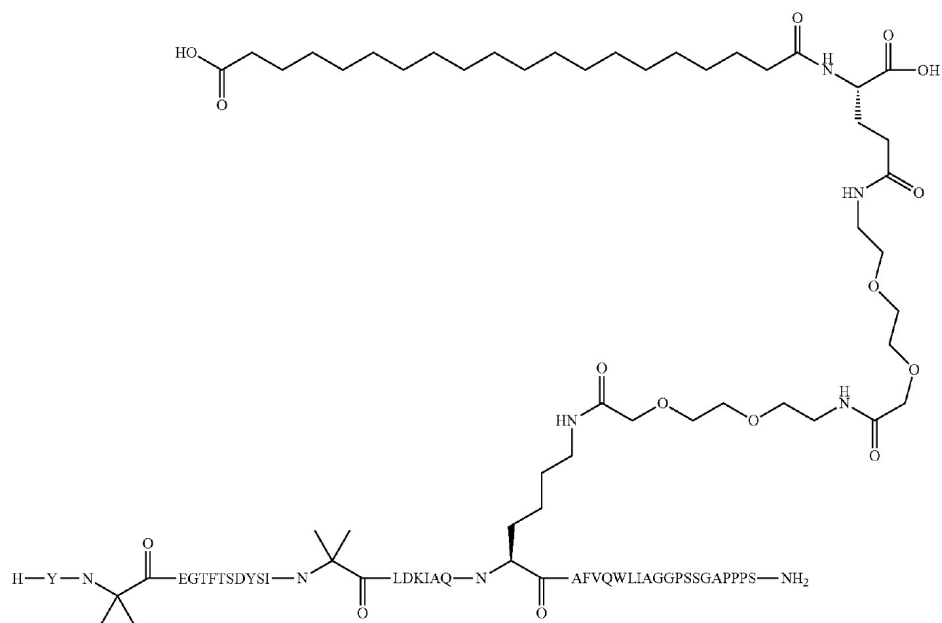
and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),

or a pharmaceutically acceptable salt thereof.

30. Claim 15 of the '780 Patent is directed to a specific compound within the genus of claim 1, as illustrated below:

15. The compound of claim 1, wherein the Formula is

¹⁸ EX1001 ('780 Patent), 41:45-44:55.



31. The compound provided in claim 15 represents tirzepatide, and is within the scope of the genus compound of claim 1, wherein the compound of Formula I has the following amino acid sequence and structural components:



wherein:

X₁ = Aib;

X₂ = Aib;

X₃ = Phe (shown as F in the sequence above);

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side chain with:

$$([2-(2\text{-Amino-ethoxy})\text{-ethoxy}]\text{-acetyl})_2\text{-(}\gamma\text{Glu)}_a\text{-CO-}$$

$$(\text{CH}_2)_b\text{-CO}_2\text{H;}$$

a = 1;

b = 18; and

the C-terminal amino acid (at position 39) is amidated as a C-terminal primary amide (NH₂).

32. In addition, the following dependent claims recite additional structural limitations, all of which are present in the specific compound of claim 15:

- claim 2 requires that the X₃ residue is Phe (F);
- claim 4 requires that b is 14 to 18 (b is 18 in the compound of claim 15);
- claim 5 requires that b is 16 to 18 (b is 18 in the compound of claim 15);
- claim 6 requires that b is 18;
- claim 7 requires that a is 1;
- claim 9 requires that the C-terminal amino acid is amidated as a C-terminal primary amide;
- claim 10 requires that X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO—(CH₂)₁₈—CO₂H; X₃ is Phe; and the C-terminal amino acid is amidated as a C-terminal primary amide.

33. Consequently, it is my understanding that a finding that the compound of claim 15 (i.e., tirzepatide) is rendered obvious by the prior art would also establish that claims 1, 2, 4-7, 9, and 10 of the '780 Patent are similarly rendered obvious by the prior art.

34. Claims 3, 8, and 11 are directed to distinct peptide compounds, and do not encompass tirzepatide. Specifically, claim 3 of the '780 Patent limits the X₃ residue to 1-Nal; claim 8 requires the number of (γGlu) units in the linker (represented by variable “a”), where a is 2; and claim 11 recites a specific compound similar to that of claim 10, except that X₃ is 1-Nal (rather than X₃ = Phe, as recited in claim 10).

35. Claims 12 and 16 recite “a pharmaceutical composition” comprising the compound of claim 10 and claim 15, respectively, in combination with “a pharmaceutically acceptable carrier, diluent, or excipient.” Claims 13 and 17 recite a method of treating type 2 diabetes, comprising administering to a patient in need thereof an effective amount of the claimed compound. Claims 14 and 18 recite combination administration with other active ingredients (i.e., metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters).

36. I discuss these limitations in my claim-by-claim analysis in Section IX.A-P.

B. The Data in the '780 Patent is Limited and Does Not Provide a Comparison to Other GIP/GLP-1 Co-Agonists

37. The '780 Patent provides a number of examples directed to the synthesis of specific peptide compounds, with varying amino acid sequences (*see* Examples 1-7).¹⁹ The '780 Patent includes only a single example (Example 8) providing an assessment of the *in vitro* and *in vivo* properties of the peptide compounds described in the patent. Specifically, Example 8 provides a number of assessments, whereby the exemplary peptides of Examples 1-8 were assessed for their binding properties to human GIP receptor, GLP-1 receptor, and glucagon receptor, as well as effective concentrations (EC₅₀), as compared to native GIP, GLP-1, and glucagon controls.²⁰ While the '780 Patent makes general reference to “control” compounds for certain assessments of the exemplary peptides,²¹ in only one instance does the '780 Patent provide testing and a comparison to a known prior art peptide.

38. Specifically, the '780 Patent provides several comparisons to the prior art semaglutide compound; however, by the '780 Patent's own admission,

¹⁹ EX1001 ('780 Patent), 8:56-13:67.

²⁰ EX1001 ('780 Patent), 16:60-17:34, Table 2.

²¹ *See* EX1001 ('780 Patent), 19:48-49 (referencing a “C18-acylated human GLP-2 control,” but not specifying the structure of the compound); and 20:63-64 (referencing a “GIP/GLP-1 co-agonist Example from WO 2011/119657,” but not explaining which of the example compounds of WO 2011/119657 was assessed, or whether the example from WO 2011/119657 was pegylated, which is known to have an adverse impact on immunogenicity).

semaglutide is a known selective GLP-1 receptor agonist (i.e., is not a co-agonist of GIP and GLP-1).²² Thus, none of the assessments provided in the '780 Patent compare the example peptides to the closest prior art, namely other GIP/GLP-1 receptor co-agonists. The '780 Patent admits that the prior art previously disclosed co-agonists of GIP and GLP-1 (“[c]ertain GIP analogs have been described as exhibiting both GIP and GLP-1 activity in WO 2013/164483, WO 2014/192284, and WO 2011/119657”).²³ The co-agonists described in these previous applications are “closer” prior art than the semaglutide compound, as these compounds were acknowledged to have co-agonist properties. The '780 Patent inventors were clearly aware of these prior art co-agonist peptides, yet elected not to include examples comparing the example peptides to other prior art GIP/GLP-1 receptor co-agonists.

39. The '780 Patent asserts that the Example 1 peptide affected murine metabolic rate compared to control, and that semaglutide “had no effect on metabolic rate.”²⁴ But again, the Example 1 peptide of the '780 Patent is a GIP/GLP-1 co-agonist, while semaglutide is not. As described in the background of the '780 Patent, both GIP and GLP-1 impact metabolic health (e.g., glucose

²² EX1001 ('780 Patent), 8:23-26.

²³ EX1001 ('780 Patent), 1:55-57.

²⁴ EX1001 ('780 Patent), 25:55-26:61.

homeostasis, insulin secretion, gastric emptying, etc.).²⁵ Consequently, a peptide that is an agonist for both GIP and GLP-1 would be expected to provide an increased metabolic response as compared to a compound that is a selective GLP-1 receptor agonist.

40. Throughout the examples, the '780 Patent provides a number of comparisons and tests between the peptides of Examples 1-8 and semaglutide (as well as comparison to non-peptide controls), as reported in Tables 7-14, provided below²⁶:

TABLE 7		
Enhancement of insulin secretion in the rat IVGTT assay		
Compound	ED ₅₀ (nmol/kg)	% max increase of insulin AUC
Example 3	1.00	314 +/- 38%
Example 3	1.42	219 +/- 19%
Example 6	2.58	289 +/- 4%
Example 7	4.33	335 +/- 35%
Example 7	1.10	278 +/- 26%
Example 8	6.13	324 +/- 30%
semaglutide	0.70	231 +/- 13%
Example 2	1.62	233 +/- 19%
Example 1	0.87	298 +/- 17%
Example 5	1.02	349 +/- 39%

²⁵ EX1001 ('780 Patent), 1:3-36.

²⁶ EX1001 ('780 Patent), 22:40-27:40.

TABLE 8

Percent body weight or fat mass change in DIO mice.			
Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-3.14 ± 0.88	-4.84 ± 1.79
Semaglutide	10	-12.36 ± 1.00****	-18.21 ± 2.24**
Semaglutide	30	-14.20 ± 1.01****	-21.90 ± 2.07****
Semaglutide	100	-19.30 ± 1.38****	-33.51 ± 3.30****
Example 3	10	-13.38 ± 0.88****	-20.76 ± 2.42****
Example 3	30	-18.13 ± 1.44****	-30.90 ± 2.06****

TABLE 8-continued

Percent body weight or fat mass change in DIO mice.			
Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Example 3	100	-25.84 ± 1.93****	-45.92 ± 2.15****
Example 6	10	-15.31 ± 1.25****	-24.75 ± 1.89****
Example 6	30	-21.62 ± 0.92****	-36.30 ± 2.47****
Example 6	100	-33.95 ± 1.93****	-64.64 ± 4.04****

**p < 0.01,

***p < 0.001,

****p < 0.0001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 9

Percent body weight or fat mass change in DIO mice.			
Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-0.74 ± 1.49	3.04 ± 3.65
Semaglutide	30	-17.03 ± 0.98****	-35.94 ± 4.09****
Example 2	10	-23.27 ± 1.72****	-49.89 ± 5.62****
Example 2	30	33.07 ± 1.65****	-72.80 ± 4.04****
Example 2	100	-34.66 ± 1.80****	-76.20 ± 3.78****
Example 5	10	-23.42 ± 1.43****	-51.28 ± 1.89****
Example 5	30	-26.84 ± 3.14****	-62.77 ± 5.49****
Example 5	100	-37.86 ± 2.25****	-81.08 ± 1.68****
Example 1	10	-25.18 ± 1.82****	-50.98 ± 2.87****
Example 1	30	-26.58 ± 2.49****	-59.98 ± 6.60****
Example 1	100	-38.14 ± 1.67****	-79.79 ± 3.10****

****p < 0.0001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 10

Percent body weight or fat mass change in DIO mice.			
Treatment	Dose (nmol/kg)	% Change from starting body weight	% Change from starting fat mass
Control	0	-2.43 ± 2.06	-1.49 ± 3.69
Example 6	10	-17.54 ± 1.17****	-34.30 ± 1.20****
Example 6	30	-19.52 ± 1.18****	-39.52 ± 3.18****
Example 6	100	-29.36 ± 2.62****	-56.66 ± 4.96****
Example 7	10	-15.08 ± 1.22****	-26.46 ± 2.31***
Example 7	30	-20.70 ± 1.95****	-43.49 ± 5.47****
Example 7	100	-24.36 ± 2.06****	-49.92 ± 3.40****
Example 8	10	-17.13 ± 0.81****	-34.20 ± 1.62****
Example 8	30	-25.27 ± 0.70****	-54.24 ± 2.35****
Example 8	100	-29.91 ± 2.03****	-65.23 ± 6.69****

****p < 0.001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 11

Blood glucose, plasma cholesterol and plasma triglycerides in DIO mice.				
Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)	Plasma Triglycerides (mg/dl)
Control	0	141.6 ± 5.59	303.2 ± 13.97	54.2 ± 11.14
Semaglutide	10	147.6 ± 6.13	226.8 ± 13.86**	27.36 ± 3.56*
Semaglutide	30	146.8 ± 8.43	229.8 ± 10.96**	27.9 ± 6.01*
Semaglutide	100	134.3 ± 9.22	218.4 ± 18.70**	36.46 ± 5.34
Example 3	10	109.5 ± 2.35***	213.2 ± 15.54***	30.38 ± 8.23
Example 3	30	107.6 ± 1.32***	177.4 ± 16.58****	21.32 ± 2.48**
Example 3	100	102.00 ± 0.50*****	194.00 ± 14.40****	20.55 ± 4.60***
Example 6	10	105.8 ± 2.10***	198.4 ± 6.76****	20.78 ± 4.40**
Example 6	30	100.1 ± 3.29*****	186.4 ± 17.04*****	26.12 ± 6.85*

TABLE 11-continued

Blood glucose, plasma cholesterol and plasma triglycerides in DIO mice.				
Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)	Plasma Triglycerides (mg/dl)
Example 6	100	103.6 ± 3.20*****	151.4 ± 14.32*****	17.26 ± 1.67***

*p < 0.05,

**p < 0.01,

***p < 0.001,

****p < 0.0001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 12

Blood glucose, plasma cholesterol and liver triglycerides in DIO mice.				
Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)	Liver Triglycerides (mg/g tissue)
Control	0	144.30 ± 8.16	233.6 ± 12.99	206.65 ± 29.47
Semaglutide	30	136.3 ± 3.81	161.0 ± 13.92***	67.63 ± 23.40****
Example 2	10	110.8 ± 3.87**	121.8 ± 13.64****	60.77 ± 13.24****
Example 2	30	110.8 ± 3.20**	114.00 ± 9.70****	65.78 ± 17.07****
Example 2	100	113.2 ± 4.86**	109.4 ± 8.83****	56.74 ± 17.76****
Example 5	10	111.00 ± 6.56**	126.6 ± 9.67****	48.30 ± 8.14****
Example 5	30	104.5 ± 5.30***	108.2 ± 13.84****	39.60 ± 4.71****
Example 5	100	105.3 ± 6.16***	108.6 ± 4.83****	67.96 ± 13.53****
Example 1	10	102.3 ± 5.59****	120.6 ± 8.55****	60.74 ± 5.33****
Example 1	30	110.7 ± 5.85**	118.2 ± 10.11****	45.24 ± 5.87****
Example 1	100	106.7 ± 7.33**	107.6 ± 10.43****	66.98 ± 17.29****

*p < 0.05,

**p < 0.01,

***p < 0.001,

****p < 0.0001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 13

Blood glucose and plasma cholesterol in DIO mice.			
Treatment	Dose (nmol/kg)	Blood Glucose (mg/dl)	Plasma Cholesterol (mg/dl)
Control	0	152.4 ± 3.63	243.6 ± 13.12
Example 6	10	121.4 ± 2.74***	167.8 ± 15.59****
Example 6	30	121.9 ± 6.65**	159.8 ± 9.99****
Example 6	100	116.1 ± 4.67****	144.2 ± 7.12****
Example 7	10	113.6 ± 4.16****	161.8 ± 6.2****
Example 7	30	114.7 ± 4.70****	153.6 ± 13.47****
Example 7	100	114 ± 2.36****	145.4 ± 9.48****
Example 8	10	114.7 ± 4.61****	158.8 ± 7.57****
Example 8	30	117.1 ± 8.26***	139.4 ± 6.83****
Example 8	100	125.4 ± 6.30**	127.8 ± 6.34****

*p < 0.05,

**p < 0.01,

***p < 0.001,

****p < 0.0001 from control group (One-Way ANOVA, Dunnett's).

The results are expressed as Mean ± SEM of 5 mice per group.

TABLE 14

Gastric emptying of a semi-liquid diet in lean C57/BL6 DIO mice.		
Treatment	Dose (nmol/kg)	Percent Gastric Emptying (Mean $\pm$ SEM)
Vehicle (n = 5)	0	69.50 $\pm$ 6.60
Semaglutide (n = 5)	30	30.56 $\pm$ 7.53**
Example 1 (n = 4)	3	49.11 $\pm$ 8.52
Example 1 (n = 5)	10	9.76 $\pm$ 7.69****
Example 1 (n = 5)	30	26.53 $\pm$ 8.14**
Example 1 (n = 5)	100	18.45 $\pm$ 6.87***

Statistical comparisons between groups are done by using one-way ANOVA followed by Dunnett's multiple comparison test.

*p <0.05,

**p <0.01,

***p <0.001,

****p <0.0001 from control group.

The results are expressed as mean $\pm$ SEM of 4-5 mice per group.

41. As is clear from the tables above, in no instance did the '780 Patent compare the peptides of Examples 1-8 to other known co-agonists of GIP and GLP-1.

42. Additionally, the data reported in the examples are all based on very small experimental groups, likely contributing to the inconsistency in results, and lack of reproducibility. For example, in Example 8, Tables 8-9, the 30 nmol/kg dose of semaglutide provided wide-ranging results, in one instance (Table 8) reporting a % change from starting body weight of -14.20 ± 1.01 , and a % change from starting fat mass of -21.90 ± 2.07 , whereas in another instance (Table 9) the '780 Patent reports that the same 30 nmol/kg dose of semaglutide provided a % change from starting body weight of -17.03 ± 0.98 , and a % change from starting

fat mass of -35.94 ± 4.09 .²⁷ A POSA will understand that achieving different results when repeating the same experiment suggests that the results are likely the product of a small test group size, and must view any such results as requiring further testing (likely with larger test group sizes) before any firm conclusions can be made based on the data.

43. Similarly, the 30 nmol/kg dose of semaglutide provided wide-ranging results when assessing the impact on blood glucose, plasma cholesterol, and plasma triglycerides, as reported in Tables 11 and 12.²⁸ Again, this would lead a POSA to view the results provided in the Examples with skepticism, and would prevent any reliable conclusions from being drawn from the data.

44. Even beyond the reproducibility issues of the data in Tables 7-14, the results of the various assessments generally suggest that the peptides of the Examples performed similarly to semaglutide. For example, the '780 Patent reports that improved glucose tolerance achieved by the Example 1 peptide was “essentially the same” as that of semaglutide, and projected that a 1 mg dose of semaglutide would be equivalent to a 1.3 mg dose of the Example 1 peptide in

²⁷ EX1001('780 Patent), Table 8 (-14.20 ± 1.01 % change in starting weight and -21.90 ± 2.07 % change in fat mass), Table 9 (-17.03 ± 0.98 % change in starting weight and -35.94 ± 4.09 % change in fat mass).

²⁸ EX1001 ('780 Patent), Table 11 (blood glucose 146.8 ± 8.43 mg/dl, plasma cholesterol 229.8 ± 10.96 mg/dl, plasma triglycerides 27.9 ± 6.01 mg/dl), Table 12 (blood glucose 136.3 ± 3.81 mg/dl, plasma cholesterol 161.0 ± 13.92 mg/dl, plasma triglycerides 67.63 ± 23.40 mg/dl).

humans.²⁹ Additionally, when the '780 Patent reported *in vivo* insulin secretion in a rat model following intravenous glucose for Example peptides 1-3 and 5-8, again compared to semaglutide, there were not any meaningful differences in activity among the GIP/GLP-1 receptor co-agonists tested.³⁰

45. In the one example where the '780 Patent attempted to assess immunogenicity, the patent failed to specify what prior art peptide the claimed peptides were being compared to (the patent only states that the peptide was compared to an example from WO 2011/119657).³¹ As an initial matter, the '780 Patent does not provide any of the underlying data that were used for this assessment (which would leave a POSA with skepticism as to the conclusions drawn from the assessment). Rather, the '780 Patent states that the peptide of Example 1 provided an EpiMatrix score (a predictive tool designed to measure potential immune response to a compound) of +1.13, which was lower than the score of +29.5 for “[a] GIP/GLP-1 co-agonist Example from WO 2011/119567,” suggesting a lower risk for immunogenicity with the peptide of Example 1. However, WO 2011/119567 discusses a number of embodiments that were PEGylated, and PEGylated drug compounds were known to have a high

²⁹ EX1001 ('780 Patent), 21:58-22:17.

³⁰ EX1001 ('780 Patent), 22:18-55, Table 7.

³¹ EX1001 ('780 Patent), 20:45-21:7.

immunogenic potential.³² Thus, a POSA would need to know the exact example peptide from WO 2011/119567 that was used for this comparison, as well as the underlying data, before any meaningful conclusions can be made.

46. Moreover, the '780 Patent discloses that the *in vivo* pharmacokinetic properties of various peptide compounds within the scope of the claims were assessed in cynomolgus monkeys.³³ The '780 Patent reports that the peptide of Example 1 provided a mean half-life of 55 hours, which was alleged to “support[] the potential of once-weekly dosing for Example 1.”³⁴ However, there are multiple issues with the reporting of this data. First, outside of a mention of the results in the specification, the '780 Patent provides little of the underlying data that was provided for Example 1 – Table 6 of the '780 Patent, which reports the test data for the peptides of Examples 2, 3, 6, 7, and 8 provides no data for the peptide of Example 1.³⁵ Additionally, Table 6 reports that the data used to assess the mean half-life was based on a treatment group size of only *two* cynomolgus monkeys (i.e., n = 2).³⁶ With such a small treatment group size, a POSA cannot make any

³² EX1022 (Garay), Abstract, 1320 (reporting that reported that up to 25% of healthy blood donors (*i.e.* no indication of ever being previously treated with a PEGylated drug), and up to 89% of patients treated with PEGylated drug have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds).

³³ EX1001 ('780 Patent), 21:10-13.

³⁴ EX1001 ('780 Patent), 21:34-37.

³⁵ EX1001 ('780 Patent), 21:34-55.

³⁶ EX1001 ('780 Patent), 21:34-55.

meaningful conclusions. Further, once again the '780 Patent failed to provide any data whereby the *in vivo* pharmacokinetic properties of Examples 1, 2, 3, 6, 7, or 8 was compared to the closest prior art, such as the GIP/GLP-1 co-agonists of WO 2013/164483, WO 2014/192284, and/or WO 2011/119657. In addition, while the '780 Patent asserts that the mean half-life of 55 hours supports potential once-weekly administration, it is nonetheless considerably less than half-life achieved with semaglutide (~160 hours), and, while semaglutide is not the closest prior art, a POSA would still not look at these values as rising to the level of a surprising or unexpected result. Consequently, the '780 Patent's reporting of *in vivo* pharmacokinetics in a very small group (i.e., n = 2; not statistically meaningful) of cynomolgus monkeys does not provide any evidence of surprising or unexpected results.

47. In total, the data provided by the '780 Patent indicates precisely what a POSA would have expected, namely that the claimed peptide compounds can be utilized as co-agonists of GIP and GLP-1, and generally provided binding affinities and other metabolic properties similar to those achieved with semaglutide.

However, none of the data in the '780 Patent demonstrates any unexpected result, much less any difference in kind, as compared to the closest prior art (i.e., other co-agonists of GIP and GLP-1).

C. Prosecution History of the '780 Patent

48. I am informed that communications between the patent applicant and the patent office (called the “prosecution history”) that led to the ’780 Patent (EX1004, excerpts) may be relevant for understanding the claims. I understand that the application that led to the ’780 Patent (U.S. Appl. No. 14/987,791; “the ’791 Application”) was filed on January 5, 2016.³⁷ I understand that the ’780 Patent asserts entitlement to an earliest possible filing date of January 9, 2015, which assertion is based on U.S. Provisional Patent Application No. 62/101,488.³⁸ For the purposes of my opinions, I have assumed the ’780 Patent has an effective filing date of January 9, 2015, and have used this date for evaluating the patentability of the claims.

49. Just 6 months after the ’791 Application was filed, the Examiner allowed the claims.³⁹ The prosecution history indicates that the Applicant received Patent Prosecution Highway designation and was therefore treated as “special.”⁴⁰ The “special” notification identified an April 25, 2016 prior art search conducted by the European Patent Office (EPO) in PCT/US2016/012124. However, the April 25, 2016 EPO search report considered only three references, only considered them

³⁷ EX1001 (’780 Patent), cover page.

³⁸ EX1001 (’780 Patent), cover page.

³⁹ EX1004 (’780 Patent Pros. Hy.), 22 (July 28, 2016).

⁴⁰ EX1004 (’780 Patent Pros. Hy.), 48-50.

as defining the general state of the art, and contained no analysis of any particular disclosures in any of them.⁴¹

50. The U.S. Examiner's consideration of the pending application was similarly brief. The U.S. Examiner considered a total of just thirteen publications, all of which were supplied by the Applicant (no additional references were identified by the Examiner).⁴²

51. The Applicant did not submit for consideration any of WO 2011/119657 ("Alsina-Fernandez," EX1007),⁴³ WO 2010/011439 ("DiMarchi," EX1017) or WO 2006/097537 ("Lau," EX1009), which are discussed in further detail below. Accordingly, the Examiner does not appear to have had the benefit of the disclosures of the combination of Alsina-Fernandez in view of DiMarchi and Lau, when considering the patentability of the '791 Application claims.

52. In allowing the claims, the Examiner discussed only one reference, U.S. Pub. No. 2015/0299281 to Just et al. ("Just"), which the Examiner identified as the "closest prior art." None of the data tables reported in the challenged patent make any comparisons to any of the peptides the Examiner identified as the

⁴¹ EX1005 (WO 2016/111971), 46-48; EX1006, (Written opinion), page 4.

⁴² EX1004 ('780 Patent Pros. Hy.), 36-39.

⁴³ Alsina-Fernandez is cited in the specification of the '780 Patent (at 1:55-57); however, the applicants did not include the reference in any IDS submissions, and Alsina-Fernandez is not listed on the face of the '780 Patent as one of the references considered by the Examiner.

“closest prior art.” In discussing this single reference, the Examiner focused on which peptides the Examiner believed the reference preferred or had actually reduced to practice rather than what that reference teaches as a whole.⁴⁴ Indeed, the Examiner cited disclosure only from paragraphs [0044] and [0111], Tables 1-2, and Formulae II(b)-(d) of the U.S. patent publication.⁴⁵

53. I discuss below in detail prior art teachings that the Examiner’s evaluation failed to consider during prosecution, including disclosures in EX1007 (Alsina-Fernandez), EX1017 (DiMarchi), and EX1009 (Lau), which demonstrate factual error in the Examiner’s conclusions.

V. LEVEL OF ORDINARY SKILL

54. I have been advised that the person of ordinary skill in the art (POSA) is a hypothetical person who is presumed to have known the relevant art at the time of the claimed invention. A POSA also is a person of ordinary creativity. I have been asked to assume that the relevant timeframe for my analysis is the time period before January 9, 2015—the earliest claimed priority date for the ’780 Patent.⁴⁶ Unless otherwise specifically noted, all of my opinions expressed here regarding the skilled artisan apply to the skilled artisan as of January 9, 2015.

⁴⁴ EX1004 (’780 Patent Pros. Hy.), pages 27-29.

⁴⁵ EX1004 (’780 Patent Pros. Hy.), pages 27-29.

⁴⁶ See Section IV.C, above.

55. By virtue of my education, experience, and training, I am familiar with the level of ordinary skill in the art of the '780 Patent. A POSA as of January 9, 2015, would typically have a Ph.D. in chemistry, organic chemistry, bioorganic chemistry, protein engineering or a related field. Skilled artisans also could include individuals with a master's degree in one of these fields plus two-to-five years of experience in peptide design. This individual may have worked in consultation with a team including, *e.g.*, a pharmaceutical chemist or a pharmacist familiar with formulating peptides for administration. This individual may have consulted with a physician with experience administering peptides for the treatment of diabetes or obesity. This level of skill is consistent with that presumed by the '780 Patent itself.⁴⁷

56. Furthermore, a POSA would have been familiar with prior art pertaining to cell signaling peptides, their biochemistry, and cell-based assays useful for interrogating peptide function, including the patents and publications discussed in this declaration. My education, experience, and training qualify me to opine as a POSA regarding the understanding of a skilled artisan at the relevant time, as I am and was by January 2015 a person of ordinary skill in the art.

⁴⁷ See Section IV.

VI. CLAIM CONSTRUCTION

57. I have been advised that the claim terms of the '780 Patent are to be given their plain and ordinary meaning, *i.e.*, the meaning that the terms would have had to a POSA at the time of the claimed invention.

58. I understand that this analysis focuses on intrinsic evidence, including how the patentee used the claim term in the claims, specification, and prosecution history. I also understand that dictionaries or other extrinsic sources may assist in determining the plain and ordinary meaning but cannot override a meaning that is unambiguous from the intrinsic evidence. I have followed these principles in my analysis throughout this declaration.

VII. BACKGROUND

A. General Knowledge Regarding Peptide Chemistry

59. Peptides are short strings of at least two amino acids linked by covalent peptide bonds (*i.e.*, amide bonds).⁴⁸ Both natural and engineered peptides can trigger a signaling pathway by interacting with the receptor for that signaling pathway.⁴⁹ Some signaling peptide ligands act as peptide hormones.⁵⁰

1) Proteinogenic Amino Acids

⁴⁸ EX1011 (Fields), 18.1.1.

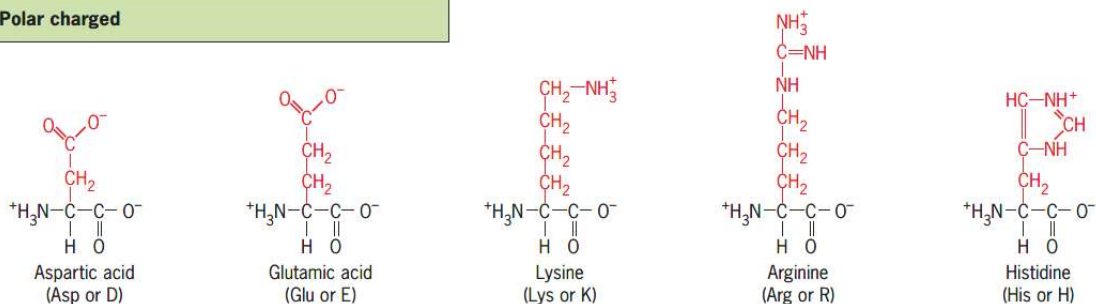
⁴⁹ EX1014 (Nelson), 118-119, 203, Fig. 5-5.

⁵⁰ *See generally* EX1015 (Segaloff).

60. Proteins in the body are naturally formed using 20 common amino acids as building blocks. Figure 2.26 below shows the chemical structures of these amino acids, as reproduced in the prior art.⁵¹

⁵¹ EX1078 (Karp), 52.

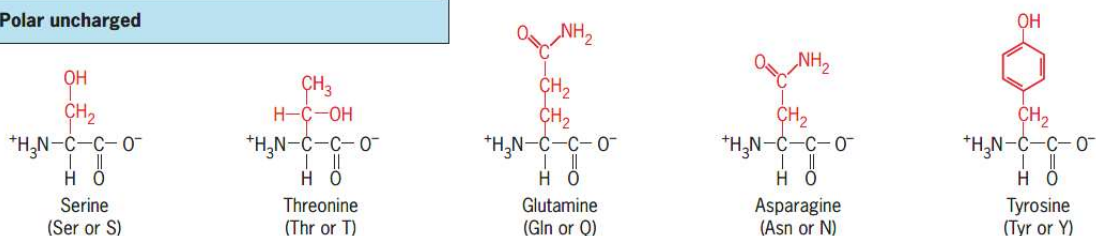
Polar charged



Properties of side chains (R groups):

Hydrophilic side chains act as acids or bases which tend to be fully charged (+ or -) under physiologic conditions. Side chains form ionic bonds and are often involved in chemical reactions.

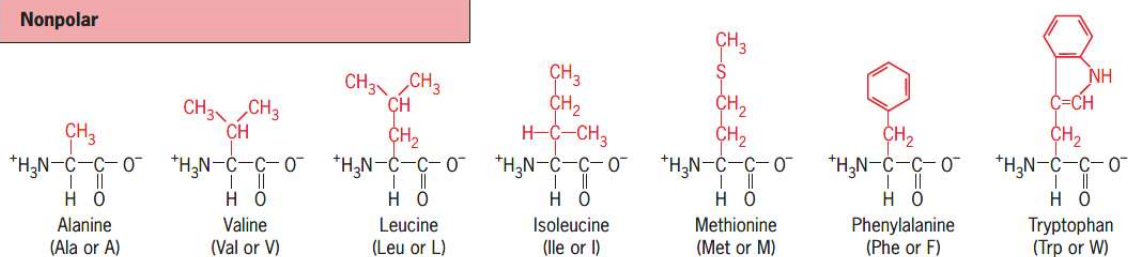
Polar uncharged



Properties of side chains:

Hydrophilic side chains tend to have partial + or - charge allowing them to participate in chemical reactions, form H-bonds, and associate with water.

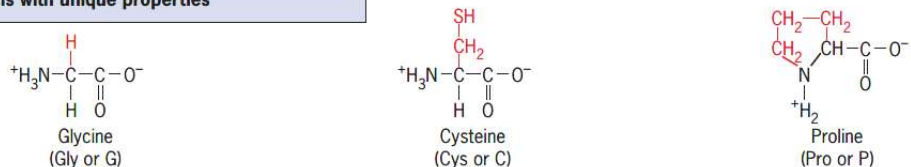
Nonpolar



Properties of side chains:

Hydrophobic side chain consists almost entirely of C and H atoms. These amino acids tend to form the inner core of soluble proteins, buried away from the aqueous medium. They play an important role in membranes by associating with the lipid bilayer.

Side chains with unique properties



Side chain consists only of hydrogen atom and can fit into either a hydrophilic or hydrophobic environment. Glycine often resides at sites where two polypeptides come into close contact.

Though side chain has polar, uncharged character, it has the unique property of forming a covalent bond with another cysteine to form a disulfide link.

Though side chain has hydrophobic character, it has the unique property of creating kinks in polypeptide chains and disrupting ordered secondary structure.

Figure 2.26 The chemical structure of amino acids. These 20 amino acids represent those most commonly found in proteins and, more specifically, those encoded by DNA. Other amino acids occur as the result of a modification to one of those shown here. The amino acids

are arranged into four groups based on the character of their side chains, as described in the text. All molecules are depicted as free amino acids in their ionized state as they would exist in solution at neutral pH.

61. As shown above, the portion of each structure shown in black represents “the backbone,” which is common to all amino acids. The portion of the structures provided in red indicate the side chains, which are the primary source of differentiation among the different amino acids.

62. These amino acid residues were regularly described using a three-letter code or a one-letter code,⁵² as illustrated in this chart:

Full	3-Letter	1-Letter	Full	3-Letter	1-Letter
Glycine	Gly	G	Phenylalanine	Phe	F
Alanine	Ala	A	Tyrosine	Tyr	Y
Valine	Val	V	Tryptophan	Trp	W
Leucine	Leu	L	Lysine	Lys	K
Methionine	Met	M	Arginine	Arg	R
Isoleucine	Ile	I	Histidine	His	H
Serine	Ser	S	Asparagine	Asn	N
Threonine	Thr	T	Glutamine	Gln	Q
Cysteine	Cys	C	Aspartate	Asp	D
Proline	Pro	P	Glutamate	Glu	E

63. The side chains of the amino acids can alter the chemical characteristics of different amino acids, sometimes impacting the function of the

⁵² EX1014 (Nelson), 118, Table 5-1.

amino acid, and, consequently, the peptides containing these amino acids. For instance, some side chains carry positive charges at physiological pH, e.g., lysine (Lys or K) and arginine (Arg or R); while others, negative charges, e.g., aspartic acid (Asp or D) and glutamic acid (Glu or E). Moreover, some side chains contain functional groups that are neutral at physiological pH and hydrophobic, e.g., leucine (Leu or L) and isoleucine (Ile or I). When two or more amino acids have similar structures and properties, each can often be replaced by others while preserving the overall structures and functions (i.e., conserved substations) as in the case for leucine and isoleucine, lysine and arginine, respectively. For example, asparagine (Asn, N) and glutamate (Glu, E), differ from one another both by the functional group on the end of the side chain (an amide vs. a carboxylic acid) and by the extent to which the terminal functional group extends from the side chain (one intermediate methylene group vs. two).⁵³

2) Peptide Synthesis

64. Synthesis of peptides was described as early as 1901,⁵⁴ however, synthesis at this stage was rudimentary and time consuming. In 1963, Robert Bruce Merrifield reported the first solid-phase peptide synthesis (SPPS) of an

⁵³ EX1014 (Nelson), 118-120.

⁵⁴ EX1011 (Fields), 18.1.1.

amino acid tetramer.⁵⁵ In 1971 he reported the SPPS of ribonuclease, a protein greater than 120 amino acids. By the 1980s, SPPS was routinely used by persons of skill in the art and regarded as the gold standard for efficient peptide synthesis, conferring multiple advantages over the formerly used methodology of synthesis in solution. These advantages included increased yield, higher throughput, and faster synthesis compared to previous methods, enabling the rapid expansion of peptide research for therapeutic applications. Moreover, the synthetic process has been automated, and peptide synthesizers have become widely available commercially. Merrifield won the 1984 Nobel Prize in Chemistry for his pioneering work in solid-phase peptide synthesis, laying a foundation for the scientific practice that became commonplace well before 2015.

3) Synthetic Analogues of Peptides as Drugs

65. Since the 1980s, those working in the field have been developing synthetic analogues of naturally occurring peptide hormones to improve stability, effectiveness, and half-life of peptide therapeutics. Breakthroughs in the synthesis of hormone mimetics such as oxytocin⁵⁶ and insulin⁵⁷ further highlighted the potential of peptide hormones as therapeutics.

⁵⁵ EX1018 (Merrifield), Abstract.

⁵⁶ EX1019 (Sawyer), 6551.

⁵⁷ EX1020 (Keen), 398.

66. Developing synthetic analogues of peptide hormones as drugs was a well-established and conventional practice by 2015. For example, the 1971 discovery of the naturally occurring 10-residue peptide hormone, Gonadotropin-Releasing Hormone (GnRH), was swiftly followed by those skilled in the art making over 2000 analogues of GnRH.⁵⁸ For GnRH, these efforts were directed to “more potent and longer acting analogs” which “were thought to be necessary for practical clinical utility.”⁵⁹

67. By 2015, modification of peptides for the purpose of improving pharmacokinetics and pharmacodynamics was routine. Skilled artisans routinely modified peptides to stabilize them against proteolysis and degradation. One approach involved PEGylation. However, this approach was known to result in undesirable immunogenicity. Specifically, in 2012, Garay et al. reported that, in contrast to the common thinking that PEG is non-immunogenic and non-antigenic, up to 25% of healthy blood donors (*i.e.* no indication of ever being previously treated with a PEGylated drug), and up to 89% of patients treated with PEGylated drug have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds.⁶⁰ The response elicited by these PEG antibodies can result in

⁵⁸ EX1021 (Karten), 44-45.

⁵⁹ EX1021 (Karten), 45.

⁶⁰ EX1022 (Garay), Abstract, 1320.

decreased therapeutic efficacy and reduced tolerance to PEGylated drug compounds.⁶¹ Consequently, a POSA approached PEGylation strategies with caution (particularly for chronic and repeated dosing), and would have been focused on other peptide development strategies.

68. A more desirable approach involved conjugation of the peptide to a lipophilic moiety. Knudsen et al. reported that the addition of fatty acid chains to the Lys20 residue of liraglutide promotes reversible binding of the peptide to albumin in the blood, decreasing degradation by DPP-IV and protracting circulation and therapeutic effect.⁶² Ward et al. disclosed that “site-specific lipidation alone could generate balanced, high potency co-agonism in glucagon-based peptides.”⁶³ Further, Zhang et al. explained that lipidation is commonly employed to improve metabolic stability, membrane permeability, and bioavailability of peptide drugs.⁶⁴ Therefore, a POSA viewed conjugation with lipophilic moieties (e.g., fatty acid chains) to be a more desirable peptide synthesis strategy, as it avoided the unwanted immunogenicity reported to be present with PEGylation, while at the same time imparting advantageous properties on the peptide, including decreased degradation by DPP-IV and prolonging circulation

⁶¹ EX1022 (Garay), Abstract, 1320.

⁶² EX1023 (Knudsen), 5.

⁶³ EX1024 (Ward), 475.

⁶⁴ EX1025 (Zhang), Abstract.

and therapeutic effect of the peptide (thereby extending the half-life and allowing for less frequent administration of the peptide).

B. Peptides as G-Protein Coupled Receptor (GPCR) Agonists and Physiologic Role in Glycemic Control and Weight Loss

69. The GLP-1 receptor, GIP receptor, and glucagon receptor are three key receptors for glycemic control that all belong to the same class (B) of the Secretin Family GPCRs.^{65,66} Class B GPCR signaling was understood by 2015 to be initiated by a two-step signaling process involving two separate domains of the receptor (“two-domain model”).⁶⁷ In the first step, specific residues of the ligand bind to the N-terminal domain (NTD) of the receptor, which imparts specificity for a particular ligand (e.g., endogenous GLP-1) to a particular receptor (e.g., endogenous GLP-1R), as compared to a ligand for a related GPCR (e.g., GIP or glucagon). In the second step, the N-terminal region of the ligand interacts with the core domain of the receptor, resulting in downstream signaling.^{68,69}

⁶⁵ EX1030 (Donnelly), 27.

⁶⁶ EX1037 (Siu), 444.

⁶⁷ EX1030 (Donnelly), 28.

⁶⁸ EX1038 (Hoare 2005), 419-420.

⁶⁹ EX1030 (Donnelly), 28.

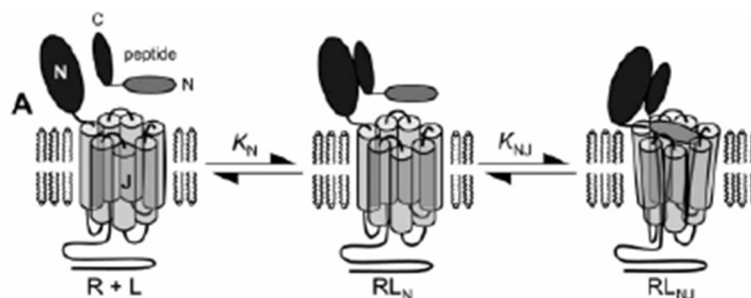


Figure 2. Adapted from Hoare S. R. (2007). Allosteric modulators of Class B G-protein coupled receptors. *Current neuropharmacology*, 5(3), 168-179⁷⁰. “Two domain model of peptide interaction with Class B GPCR’s A. Schematic representation of the two-domain model. The carboxyl-terminal portion of the peptide binds the extracellular N-terminal domain (N-domain) of the receptor, forming RL_N , defined by the equilibrium constant K_N . This interaction acts as an affinity trap, promoting interaction of the amino-terminal portion of the ligand with the juxtamembrane domain (J-domain) of the receptor, forming RL_{NJ} . The J-domain interaction is defined by the isomerization constant K_{NJ} defining the $RL_{NJ} : RL_N$ concentration ration.”

1) Incretin GPCR Ligands – GIP and GLP-1

70. GIP and GLP-1 are both incretins (insulin-promoting hormones) that exist naturally in the body.⁷¹ The body is designed to release them postprandially, among other things, to convey satiety (i.e., the feeling of being full).⁷² GIP was first discovered in 1989 for its ability to inhibit gastric secretion.^{73,74} The 42-amino

⁷⁰ EX1039 (Hoare 2007), 170.

⁷¹ EX1040 (Seino), 8-9.

⁷² EX1040 (Seino), 8-9.

⁷³ See generally EX1041 (Brown).

⁷⁴ EX1042 (Inagaki), 1014, 1016-1017.

acid peptide was later found to stimulate pancreatic insulin secretion in healthy human volunteers⁷⁵ by stimulating pancreatic beta cells.⁷⁶ With the stimulation of insulin release, GIP was able to improve glucose tolerance and improve physiological response to high blood sugar,⁷⁷ providing a potential mechanism for control of hyperglycemia.

71. In the early 1980's, Joel Habener and Svetlana Mosjov discovered a 37-amino acid Glucagon-like peptide-1 (GLP-1) hormone.⁷⁸ The peptide stimulated insulin secretion and suppressed glucagon secretion to regulate blood sugar levels.⁷⁹ GLP-1(1-37) is expressed in intestinal L cells and is derived from cell-specific post-translational processing of the pre-proglucagon gene.⁸⁰

72. In 1987, Mosjov et al. and others discovered that the 37-residue GLP-1 peptide was actually a pro-peptide that was activated by cleavage of the first six N-terminal residues, leaving a conserved histidine as the N-terminal residue of the active form of GLP-1(7-37).⁸¹ In fact, these two N-terminally truncated products (GLP-1(7-37) and GLP-1(7-36) amide) are the active species *in vivo*, are

⁷⁵ EX1043 (Dupre), Abstract.

⁷⁶ EX1044 (Adrian), 414.

⁷⁷ EX1043 (Dupre), Abstract.

⁷⁸ *See generally* EX1045 (Lund).

⁷⁹ *Id.*

⁸⁰ EX1030 (Donnelly), 27.

⁸¹ *Id.*

equipotent to one another, are the major physiological incretin in humans, and are commonly referred to as the endogenous form of GLP-1⁸². Accordingly, amino acid residue numbering for endogenous GLP-1 often is performed using the convention of positions (1-30) or (1-31)—referring to the positions of the active peptide—rather than positions (7-36)/(7-37) of the pro-peptide. In addition to increasing insulin secretion and expression, endogenous GLP-1 inhibits beta-cell apoptosis, promotes beta-cell neogenesis, reduces glucagon secretion, delays gastric emptying, promotes satiety, and increases peripheral glucose disposal, thus playing a central role in controlling postprandial blood sugar levels.⁸³

73. There were two primary limitations on the use of exogenous GLP-1 for the treatment of diabetes and obesity: (1) a very short half-life (only a few minutes); and (2) rapid degradation, with functional loss by DPP-IV-catalyzed cleavage of the two N-terminal residues (1-2) of the active form (residues 7-8 of the pro-peptide).^{84,85} Though some forms of endogenous peptide cleavage activate GLP-1 (i.e., cleaving N-terminal residues 1-6 of the pro-peptide), other forms essentially deactivate it. In particular, studies identified a dipeptidyl peptidase (DPP)-IV cleavage site at pro-peptide residue 8 (Ala), where active GLP-1 is

⁸² EX1030 (Donnelly), 27.

⁸³ EX1030 (Donnelly), 27-28.

⁸⁴ EX1030 (Donnelly), 28.

⁸⁵ EX1046 (Hui), Abstract.

cleaved into GLP-1(9-37) or GLP-1(9-36)amide,⁸⁶ a much less active form with lower affinity for the GLP-1 receptor.^{87,88,89} In parallel, Kieffer et al. demonstrated the absence of both GLP-1 and GIP degradation and improved GIP/GLP-1 activity in DPP-IV deficient rodents.⁹⁰ Kieffer and Mosjov's work thus paved the way for using modified synthetic GLP-1 and GIP peptides (substituted at position 2 of the activated peptide to decrease DPP-IV cleavage) for therapeutic use in diabetes, obesity, and cardiovascular health.

2) Diabetes and Obesity Treatment Using GLP-1 Agonists

a) Incorporation of the Exendin Tail to Minimize DPP-IV Degradation and Extend Half-Life

74. As I noted above, by the 1980's considerable work was being done on the development of GLP-1 agonist peptide compounds. Specifically, researchers studying the saliva of a Gila monster (a venomous lizard), and trying to ascertain why the Gila monster eats very rarely, discovered the endogenous GLP-1-receptor agonist exendin-4, which is resistant to DPP-IV cleavage largely because the Ala² is replaced with Gly², a DPP-IV resistant amino acid.⁹¹ Discovery of the natural

⁸⁶ The numbering in GLP-1(9-37) and GLP-1(9-36) refers to the positions in the pro-peptide.

⁸⁷ EX1047 (Singh), 753754.

⁸⁸ EX1048 (Kieffer), 3587, Figure 1.

⁸⁹ EX1049 (Montrose-Rafizadeh), 21204, Table I.

⁹⁰ EX1048 (Kieffer), 3587, Figure 1.

⁹¹ EX1030 (Donnelly), 28.

GLP-1 receptor agonists derived from Gila monster saliva led to rapid exploration of the SAR explaining both the superior potency⁹² and proteolytic stability⁹³ of the exendin-3 and -4 (sequences shown below) peptides as compared to GLP-1 and GIP. Exendin-3 and -4 differ from one another only by the residues employed at positions 2 and 3. In the annotated figure below, I have shown the differing amino acid residues of Exendin-3 and Exendin-4 (highlighted in yellow), and also the C-terminal motif (highlighted in blue).⁹⁴

EXENDIN-3	HSDGTFTSDLSKQMEEEAVRLFIEWLKN	GGPSSGAPPPS
EXENDIN-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKN	GGPSSGAPPPS

75. The superior metabolic stability and GLP-1 receptor agonist activity of exendins was also traced specifically to the C-terminal motif, which forms a Trp-cage motif or fold.⁹⁵ Adding the C-terminal motif (i.e., the exendin extension) to DPP-IV-resistant GLP-1 significantly improved its affinity and biological activity for GLP-1 receptor agonism as well as its metabolic stability against

⁹² EX1069 (Thum), 8 (The GLP-1 homologs exendin-3 and -4 both “share the biological properties of GLP-1” with only 50% homology to GLP-1, and with exendin-4 being “much more potently insulinotropic than GLP-1.”).

⁹³ EX1069 (Thum), Abstract, 7 & Table 4 (initial rates of proteolysis were 655 M/min/mg BBMM for GLP-1, 600 for GIP, 1 for Exendin-4, and 0.82 for Exendin-3). GIP and GLP-1 “differ little in their susceptibility to proteolysis by these ectopeptidases.” *Id.*, 7. Both “exhibit remarkable stability in the presence of mammalian ectopeptidases” and exendin-4 “exhibits high metabolic stability, which is already suggested by its very long-acting effects in vivo.” *Id.*, 8.

⁹⁴ EX1069 (Thum), 6, Table 1.

⁹⁵ EX1072 (Doyle), Abstract, 157.

neutral endopeptidases.⁹⁶ The formation of the Trp-cage fold by the C-terminal motif additionally was understood to provide metabolic stability to the peptides, by reducing the rate at which the peptides were cleared by the kidneys and peripheral tissues.⁹⁷ Adding the C-terminal motif to GLP-1 significantly reduced its rate of clearance while maintaining GLP-1 receptor binding and activation properties resembling native GLP-1.⁹⁸ Researchers hypothesized that the reduced clearance rate of the extended GLP-1 analogue (employing the C-terminal motif of exendin) may result from reduced receptor-endocytosis-mediated clearance.⁹⁹

76. Researchers subsequently demonstrated that the C-terminal motif similarly improved proteolytic resistance and insulintropic activity of GIP without adversely affecting binding potency or functional activity at the GIP receptor relative to native GIP or DPP-IV-resistant GIP.¹⁰⁰ Researchers proposed that the random, flexible coil provided by the endogenous GIP C-terminal motif was

⁹⁶ *Id.*, Abstract, 155-157.

⁹⁷ EX1073 (Simonsen), Abstract.

⁹⁸ *Id.*, Abstract, 17-20 & Table 2; *id.*, 20 (“The present study clearly indicates that the COOH-terminal extension of EX-4 must provide some protection, since the renal clearance of GLP-1 was reduced to an amount closer to and not significantly different from the glomerular filtration rate when this sequence was added to GLP-1.”).

⁹⁹ *Id.*, 21 (“Widman showed that GLP1 is internalized following binding but EX9-39 is not internalized even though it binds to the receptor. It could, therefore, be speculated that the additional renal extraction of GLP-1 is due to the receptor mediated internalization of the peptide which does not take place for EX-4 and is prevented if the COOH-terminal tail from EX-4 is added to GLP-1.”).

¹⁰⁰ EX1074 (Tatarkiewicz), Abstract, 75-79, 82-84 & Table 1 (discussing C-terminally extended GIP analogue AC163794).

responsible for undesirable lipogenic activity of GIP, and thus proposed replacing it with the exendin C-terminal motif to avoid undesirable lipogenesis.¹⁰¹

77. The knowledge of the advantages of the exenatide C-terminal tail (which, as noted, forms the Trp-cage motif) resulted in the development of multiple peptide drug compounds utilizing this very strategy, such as lixisenatide (Lyxumia[®] and Adlyxin[®]) and exenatide (originally approved by the FDA in 2005 as Byetta[®] and later as an extended release formula, Bydureon[®]).¹⁰² Exenatide is a synthetic form of the naturally existing 39-amino acid exendin-4 peptide isolated from the saliva of the Gila monster (a lizard). Compared to human GLP-1, exenatide binds to the receptor with similar affinity, yet is refractory to *in vivo* degradation, thereby having a much longer half-life. The resistance to degradation by the DPP-IV peptidase is attributed to the difference in the second amino acid (Ala in GLP-1 and Gly in exenatide), and the additional overall stability of the peptide structure conferred by the C-terminal extension or tail in exenatide (which forms the Trp-cage motif, specifically between the Trp²⁵ and the C-terminal sequence -GGPSSGAPPPS). Exenatide was reported as having a half-life of

¹⁰¹ EX1074 (Tatarkiewicz), 82 (“GIP tail is a flexible random coil, recently suggested to have lipogenic function....The replacement of this tail region with a unique C-terminus tail of exenatide resulted in AC163794...with a significantly longer duration of insulinotropic action compared with native GIP or the DPP-IV resistant D-ala² GIP1-42 peptide.”).

¹⁰² EX1054 (BYETTA).

approximately 2.4 hours,¹⁰³ which was a significant enhancement over native GIP and GLP-1, having half-lives on the order of minutes.

78. Critical for further drug development, the crystal structures of exenatide and its complex with glucagon-like peptide-1 receptor (GLP-1R) were solved prior to 2015, paving the pathway for structure-based rational design.¹⁰⁴ For instance, the authors noted “[t]he Trp cage of Exendin-4 is not involved in binding to nGLP-1R. The hydrophobic binding site of nGLP-1R is defined by discontinuous segments including primarily a well-defined α -helix in the N terminus of nGLP-1R and a loop between two antiparallel β -strands.”¹⁰⁵

79. Another peptide drug compound that was developed utilizing the exendin tail motif was lixisenatide. Though lixisenatide¹⁰⁶ (derived from exendin-4) first received FDA approval for diabetes after the January 2015 priority date, it was heavily discussed in the literature before the January 9, 2015 critical date.¹⁰⁷ Like exenatide, lixisenatide incorporated the same exendin tail, which again, forms the Trp-cage motif, rendering the peptide more resistant to degradation by DPP-IV, and also extends the half-life of the compound.

¹⁰³ EX1054 (Byetta), 3.

¹⁰⁴ See EX1082 (Runge).

¹⁰⁵ See EX1082 (Runge), abstract, 11342.

¹⁰⁶ EX1056 (“ADLYXIN”), 1-2, 11.

¹⁰⁷ EX1058 (Monami), Abstract, 2.

b) Conjugation with Lipophilic Fatty Acids to Enhance Albumin Binding and Further Extend the Half-Life

80. While the incorporation of the C-terminal exendin tail motif was a common design choice to protect against DPP-IV degradation, and to extend the half-life of GLP-1 agonist peptides, other design peptide design strategies had also become commonplace. In 2007, Madsen et al. examined the impact of conjugating fatty acids, and fatty acid chain length on the half-life and duration of GLP-1 compounds.¹⁰⁸ Specifically, Madsen assessed various peptide derivatives, all of which were derivatized at the lysine (K) at position 26 of the native GLP-1 sequence (corresponding to position 20 of the GLP-1 agonist compound sequence, I have discussed previously) with a spacer and an acyl group.¹⁰⁹ This is the same conjugation strategy I discussed previously. Additionally, Madsen utilized a γ -Glu spacer in Compounds 1-6, which was attached to fatty acids of varying lengths, including C10, C11, C12, C14, C16, and C18 fatty acids (corresponding to Compounds 1, 2, 3, 4, 5, and 6, respectively).¹¹⁰ Madsen found that, as the length of the fatty acid attached to the spacer increases, the compound's half-life also increases, with half-life values of 0.8 hours for the C10 fatty acid; 5.1 hours for the

¹⁰⁸ See EX1079 (Madsen).

¹⁰⁹ EX1079 (Madsen), 6126-6127.

¹¹⁰ EX1079 (Madsen), 6127.

C11 fatty acid; 7.6 hours for the C12 fatty acid; 9 hours for the C14 fatty acid; 16 hours for the C16 fatty acid; and 21 hours for the C18 fatty acid.¹¹¹

81. In view of this additional research and understanding, as exemplified by Madsen, many peptide drug compounds began to incorporate fatty acids as a strategy to further extend the half-life of GLP-1 agonist peptides. One such example is the synthetic GLP-1 agonist liraglutide^{112,113} which was developed and engineered to have 97% sequence identity to the active portion of endogenous GLP-1 (amino acids 7-37), the sole difference being the substitution of an arginine amino acid in place of a lysine amino acid at position 28 of the aligned peptide (pro-peptide position 34).¹¹⁴ Liraglutide further includes a C-16 fatty acid (palmitic acid) attached to the peptide with a gamma glutamate (γ Glu) spacer at the epsilon-amino group of the lysine at position 20 (pro-peptide position 26) of the peptide base sequence.

82. Additionally, it was known by December 2014 that semaglutide was a GLP-1 derivative for once-weekly administration that was under development by Novo Nordisk A/S.¹¹⁵ Semaglutide is a 31 amino acid peptide hormone, with two

¹¹¹ EX1079 (Madsen), 6127.

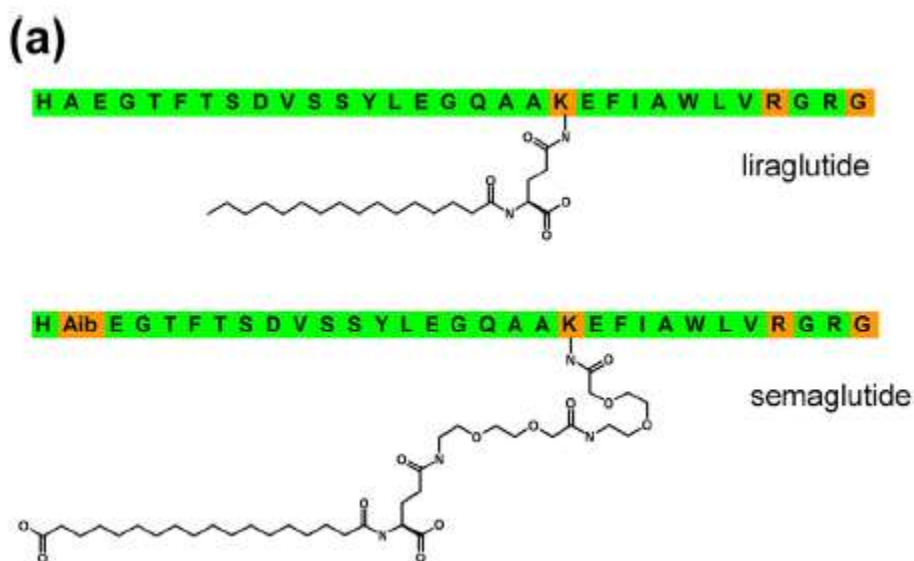
¹¹² EX1050 (“VICTOZA”), 1, 11.

¹¹³ EX1013 (“SAXENDA”), 1, 14.

¹¹⁴ EX1051 (Bode), Abstract, S59; EX1050 (“VICTOZA”), 1, 11-12.

¹¹⁵ See, e.g., EX1010 (WO 2014/202727), 1:21-23; EX1009 (Lau), Example 4.

amino acid substitutions as compared to native GLP-1, namely Ala is substituted with Aib at position 2 (pro-peptide position 8), and Lys is substituted with Arg at position 28 (pro-peptide position 34).¹¹⁶ Semaglutide also incorporates a C18-diacid fatty acid chain attached via an AEEA-AEEA- γ Glu spacer to the Lys at position 20 (pro-peptide position 26).^{117,118} To illustrate, the structures of both liraglutide and semaglutide are shown below:¹¹⁹



¹¹⁶ EX1078 (Lorenz), 4014.

¹¹⁷ EX1078 (Lorenz), 4014.

¹¹⁸ A POSA would know and understand that the terms “fatty acid” and “fatty diacid” are considered interchangeable in the context of the fatty acid chain conjugated to the GIP/GLP-1 peptides. Indeed, the prior art uses the terms interchangeably (*see, e.g.*, Lorenz, which refers to semaglutide’s conjugation with a “fatty acid,” but clearly illustrates in Fig. 2a that a C18 fatty diacid is conjugated). Indeed, even the ’780 patent only refers to conjugation with “fatty acids,” but the claims clearly contemplate conjugation with fatty diacids, suggesting the two terms and concepts are interchangeable. Thus, consistent with this understanding, I have used these terms interchangeably, and the prior art discussion of conjugation with “fatty acids” is known to include conjugation with fatty diacids, and vice versa, unless specified otherwise.

¹¹⁹ EX1078 (Lorenz), 4014, Fig. 2a.

83. The development of liraglutide and semaglutide, both with prolonged half-lives, represented a growing trend in the field of peptide design and synthesis, namely the conjugation of lipophilic fatty acids to GLP-1 agonist peptides (specifically at the lysine 20 position) to prolong the half-life and allow for extended dosing schedules. As explained by Lorenz et. al., fatty acid conjugation was a well-established strategy to prolong the action of peptides by facilitating binding to serum albumin, thereby reducing the renal clearance of the peptide.¹²⁰ Liraglutide and semaglutide are two examples of this design strategy. As noted, liraglutide includes a C16 fatty acid conjugated to the Lys at position 20 via a glutamate spacer, resulting in extensive binding to serum albumin (~99%), leading to increased enzymatic stability towards DPP-IV, while reducing renal clearance.¹²¹ This substantial binding results in a plasma half-life of 11-13 hours, which is substantially longer than native GLP-1 (known to have a short half-life of ~ 2 minutes).¹²² Semaglutide similarly includes a C18-diacid fatty acid chain also conjugated to the Lys at position 20, resulting in significant serum albumin binding, and an even longer half-life of ~160 hours.¹²³

C. Rational Design of GLP-1/GIP Co-Agonists

¹²⁰ EX1076 (Lorenz), 4014.

¹²¹ EX1076 (Lorenz), 4014.

¹²² EX1076 (Lorenz), 4013-14.

¹²³ EX1076 (Lorenz), 4014.

84. By late 2014, GLP-1 and GIP co-agonist peptides were being explored, both *in vitro* and *in vivo*.^{124,125} Notably, Finan et al. described a GLP-1/GIP co-agonist which exhibited “enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists.”¹²⁶ Many other references had also begun to investigate and disclose various GIP/GLP-1 co-agonists, including Alsina-Fernandez,¹²⁷ DiMarchi,¹²⁸ and Just,¹²⁹ among others. In particular, Finan describes refining the duration of action of the co-agonists through site-specific lipidation to support less frequent administration.¹³⁰ In fact, Finan et al. had established core sequences that would lead to GLP-1/GIP co-agonism without

¹²⁴ EX1059 (Day), 754, Figure 5-6.

¹²⁵ *See generally* EX1061 (Finan).

¹²⁶ EX1061 (Finan), Abstract, 1.

¹²⁷ *See* EX1007 (Alsina-Fernandez).

¹²⁸ *See* EX1017 (DiMarchi).

¹²⁹ *See* EX1008 (Just).

¹³⁰ EX1061 (Finan), Abstract, 5-6.

glucagon agonism, and described these sequences in Supplemental Figure 1¹³¹:

Glucagon	HSQGTFTSDYSKYLD ~~SRRAQ~~ DFVQWLMNT-OH
GIP	YAEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-OH
GLP-1	HAEGTFTSDVSSYLEGQAAKEFIAWLVKGRG-OH
Exendin-4	HGEGTFTSDLSKQMEEEAVRLFIEWLKNGGPSSGAPPPS-NH ₂
Liraglutide	HAEGTFTSDVSSYLEGQAAK ^a EFIAWLVRGRG-OH
Peptide 3	HAEGTFTSDVSKYLEEQAAKEFIAWLVKGGPSSGAPPPSK-NH ₂
Peptide 6	YXEGTFISDYSIAMDKIHQQDFVNWLLAQKGKKNDWKHNITQ-NH ₂
Peptide 7	YXEGTFISDYSIAMDKIHQQDFVNWLLAQGPSSGAPPPSK ^b -NH ₂
Peptide 9	HXQGTFTISD ~~K~~ ^c SKYLDXRAAQDFVQWLMDT-OH
Peptide 10	HSQGTFTSDYSKYLD <u>EQAAKE</u> FIWLMNT-NH ₂
Peptide 11	HSQGTFTSDYSKYLD <u>EIQKE</u> FIWLMNT-NH ₂
Peptide 12	HSQGTFTSDYSKYLD <u>EQAAKE</u> FIWLMNGGPSSGAPPPS-NH ₂
Peptide 13	YSQGTFTSDYSKYLD <u>EQAAKE</u> FIWLMNGGPSSGAPPPS-NH ₂
Peptide 14	YSQGTFTSDYSKYLD <u>EQAAKE</u> FVNWLLAGGPSSGAPPPS-NH ₂
Peptide 15	YXQGTFTSDYSIYLD <u>EQAAKE</u> FVNWLLAGGPSSGAPPPS-NH ₂
Peptide 16	YXQGTFTSDYSIYLD <u>EQAAKE</u> FVNWLLAGGPSSGAPPPSC-NH ₂
Peptide 17	YXEGTFTSDYSIYLD <u>QAAKE</u> FVNWLLAGGPSSGAPPPSC-NH ₂
Peptide 18	YXEGTFTSDYSIYLD <u>QAAKE</u> FVNWLLAGGPSSGAPPPSK-NH ₂
Peptide 19	YXEGTFTSDYSIYLD <u>QAAKE</u> FVNWLLAGGPSSGAPPPSK ^b -NH ₂
Peptide 20	YXEGTFTSDYSIYLD <u>QAAKE</u> FVCWLLAGGPSSGAPPPSK-NH ₂
Peptide 21	YXEGTFTSDYSIYLD <u>QAAKE</u> FVC [*] WLLAGGPSSGAPPPSK-NH ₂

X=aminoisobutyric acid =lactam
K^a=Lys-γE-C₁₄ acyl K^b=Lys-C₁₄ acyl K^c=Lys-γEγE-C₁₄ acyl C^{*}=Cys-40kDa PEG

85. As can be seen in Supplemental Figure 1, Finan incorporated the exendin C-terminal tail (i.e., Trp cage motif) in the majority of its peptide compounds (e.g., peptides 12-21), similar to the strategy adopted in the development of exenatide and lixisenatide.

86. Additionally, DiMarchi, another reference focused on GIP/GLP-1 co-agonists, had also begun to investigate these same peptide design strategies as early as 2009. Specifically, DiMarchi discloses that increased activity at the GLP-1

¹³¹ EX1061 (Finan), Supplemental Figure 1.

receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS or XGPSSGAPPPS to the C-terminus (i.e., the extendin C-terminal tail).¹³² In particular, DiMarchi reports that glucagon peptides having a glycine substitution for threonine at position 29 and the C-terminal extension of GPSSGAPPPS is *four times* as potent at the GLP-1 receptor as native glucagon modified to include the C-terminal extension.¹³³

87. DiMarchi further teaches that the peptide compounds can be further modified to “[i]ncreas[e] solubility and/or duration of action or half-life in circulation and/or delaying the onset of action by acylation or alkylation of the glucagon peptide, as described herein.”¹³⁴ DiMarchi explains that the peptides can be acylated via a spacer¹³⁵, and that the acyl group can include fatty acids ranging from C4 to C30 fatty acids.¹³⁶

88. Consequently, while the development of GIP/GLP-1 co-agonists was in its earlier phases prior to January 2015, the art was clear that these co-agonists could be developed with efficacy in the treatment of diabetes and for weight loss. It was also clear to a POSA that the rational design strategies utilized to extend half-

¹³² EX1017 (DiMarchi), 5:7-11.

¹³³ EX1017 (DiMarchi), 55:10-15.

¹³⁴ EX1017 (DiMarchi), 8:12-14.

¹³⁵ EX1017 (DiMarchi), 7:7-12.

¹³⁶ EX1017 (DiMarchi), 64:7-13

life with GLP-1 selective peptide compounds could be similarly utilized with GIP/GLP-1 co-agonist peptide compounds, namely:

- **the incorporation of the C-terminal exendin tail to protect against degradation by DPP-IV, increase potency and overall structural stability, and to extend half-life; and**
- **conjugation (preferably at the lysine 20 position) with a lipophilic fatty acid to promote albumin binding and further extend the half-life.**

89. Based on the utilization of these design strategies in the development of other FDA-approved drug compounds, these strategies would have been a primary focus for a POSA looking to achieve similar results related to protecting against degradation by DPP-IV, and extending the peptide's half-life.

VIII. SUMMARY OF THE PRIOR ART REFERENCES

90. I have reviewed several references that published before January 9, 2015, and which teach or suggest the compounds recited in the claims of the '780 Patent. I understand that these references may be considered in evaluating the patentability of the claims of the '780 Patent.

A. WO 2011/119657 A1 (Alsina-Fernandez, et al.)

91. International Publication No. WO 2011/119657, entitled "NOVEL PEPTIDES AND METHOD FOR THEIR PREPARATION AND USE" ("Alsina-Fernandez") published on September 29, 2011, based on applications filed by Eli Lilly & Co. on March 23, 2011 (International Application No. PCT/US2021/029501) and March 26, 2010 (U.S. Provisional Application No. 61/317,850). Accordingly, I have been advised that Alsina-Fernandez is prior art to the '780 Patent. The first named inventor, Jorge Alsina-Fernandez, is also a named inventor on the '780 Patent.

92. Alsina-Fernandez discloses an invention in the field of treatment of diabetes and relates to peptides that exhibit activity for both the GIP and GLP-1 receptors, and are selective over the glucagon receptor.¹³⁷ Alsina-Fernandez discloses that GIP and GLP-1 are known incretins, that incretin receptor signaling

¹³⁷ EX1007 (Alsina-Fernandez), Abstract.

exerts physiologically relevant actions critical for glucose homeostasis.¹³⁸ Alsina-Fernandez further discloses that GIP has been shown to stimulate insulin secretion from pancreatic beta cells in the presence of glucose, and GLP-1 protects pancreatic beta cells and inhibits glucagon secretion, gastric emptying and food intake which lead to weight loss.¹³⁹ Alsina-Fernandez also discloses that glucagon signals the liver to release glucose causing an increase in blood glucose.¹⁴⁰ Therefore, Alsina-Fernandez discloses that stimulation of the glucagon receptor is undesirable in diabetic patients.¹⁴¹

93. Alsina-Fernandez discloses that GLP-1 is effective at lowering glucose in both healthy and diabetic subjects, but that using it at full efficacy causes nausea.¹⁴² Thus, Alsina-Fernandez states that there is a need to develop new peptides which “potentiate insulin secretion in a glucose-dependent manner,” “possess the glucose-lowering effects of GLP-1 without the nausea,” and “have increased metabolic stability.”¹⁴³ Accordingly, Alsina-Fernandez provides “new potent and efficacious peptides with amino acid substitution introduced to modulate activity for both GIP and GLP-1 while maintaining selectivity over

¹³⁸ EX1007 (Alsina-Fernandez), 1:8-21.

¹³⁹ EX1007 (Alsina-Fernandez), 1:9-13.

¹⁴⁰ EX1007 (Alsina-Fernandez), 1:15-16.

¹⁴¹ EX1007 (Alsina-Fernandez), 1:16-17.

¹⁴² EX1007 (Alsina-Fernandez), 1:21-23.

¹⁴³ EX1007 (Alsina-Fernandez), 1:32-2:4.

glucagon” to use the glucose-lowering effects of GLP-1 to better harness the insulin-secretion effects of GIP.¹⁴⁴ Alsina-Fernandez teaches that administration of these peptides is useful for reducing body weight, in addition to increasing glucose sensitivity.¹⁴⁵

94. A specific GIP analogue peptide disclosed to have a favorable balance of GLP-1 and GIP agonism for treating diabetes and reducing body weight is disclosed as SEQ ID NO: 1.¹⁴⁶ As set forth by Alsina-Fernandez, the first 28 amino acid residues of SEQ ID NO: 1 are:

Tyr¹ Aib² Glu³ Gly⁴ Thr⁵ Phe⁶ Thr⁷ Ser⁸ Asp⁹ Tyr¹⁰ Ser¹¹ Ile¹² Aib¹³ Leu¹⁴ Asp¹⁵

Lys¹⁶ Ile¹⁷ Ala¹⁸ Gln¹⁹ Arg²⁰ Ala²¹ Phe²² or 1-Nal²² Val²³ Gln²⁴ Trp²⁵ Leu²⁶ Ile²⁷

Ala²⁸.¹⁴⁷ SEQ ID NO: 1 also comprises a C-terminal tail having the following

sequence: Aib K G K Q E W K H Q I T Q and optionally one or two PEGylated

cysteine residues, with the C-terminal amino acid optionally amidated.¹⁴⁸ Alsina-

Fernandez teaches that the peptides are stable against rapid metabolic deactivation

¹⁴⁴ EX1007 (Alsina-Fernandez), 2:5-8.

¹⁴⁵ EX1007 (Alsina-Fernandez), 2:9-10.

¹⁴⁶ EX1007 (Alsina-Fernandez), Abstract, 2:12-20 (“The present invention provides a peptide comprising the sequence ... (SEQ ID NO: 1)”), Claims 1-12.

¹⁴⁷ EX1007 (Alsina-Fernandez), 2:12-25, 5:24-27.

¹⁴⁸ EX1007 (Alsina-Fernandez), 2:12-25.

by DPP-IV.¹⁴⁹ Alsina-Fernandez teaches routine methods for making the peptides.¹⁵⁰

95. Alsina-Fernandez teaches the peptides have binding affinity (K_i) to GIPR and GLP-1R of lower than 100 nM, a ratio of GIP/GLP-1 binding activity of 4:1 to 1:2 (ranging from 4x higher affinity for GIPR to 2x higher affinity for GLP-1R), and a selectivity ratio versus glucagon-R of at least 100 times.¹⁵¹ The K_i value is an indicator of binding affinity. The lower the K_i value, the stronger the binding affinity.

96. Alsina-Fernandez reports results of a GIPR binding assay that demonstrate that all peptides of Table 1 bind to GIPR and may activate that receptor, in turn triggering GIP-dependent physiological responses.¹⁵² The K_i values ranged from 0.023 nM to 9.79 nM, with the strongest binding affinity provided by Example peptides 1 and 2 (Phe²² or 1-Nal²² peptides lacking C-terminal Cys residues and PEGylation) as compared to Example peptides 3-5 (PEGylated C-terminal Cys residues).¹⁵³

¹⁴⁹ EX1007 (Alsina-Fernandez), 5:22-23.

¹⁵⁰ EX1007 (Alsina-Fernandez), 7:7-8:5.

¹⁵¹ EX1007 (Alsina-Fernandez), 11:20-27.

¹⁵² EX1007 (Alsina-Fernandez), 11:29-13:10.

¹⁵³ EX1007 (Alsina-Fernandez), 13:7-8 & Table 1.

97. Alsina-Fernandez reports results of a GLP-1-R binding assay that it says demonstrates that all peptides of Table 2 bind to GLP-1-R and may activate that receptor, in turn triggering GLP-1-dependent physiological responses.¹⁵⁴ The K_i values ranged from 0.059 nM to 9.00 nM, with the strongest binding affinity by Example peptides 1 and 2 (Phe²² or 1-Nal²² peptides lacking C-terminal Cys residues and PEGylation) as compared to Example peptides 3-5 (PEGylated C-terminal Cys residues).¹⁵⁵ In each case, the K_i value reported for the Phe²² analogue was similar though nominally lower than that for the 1-Nal²² analog. (0.023 nM vs. 0.044 nM; 0.059 nM vs. 0.096 nM).

98. Alsina-Fernandez reports results of a glucagon-R binding assay that it says demonstrates that no peptides of Table 3 initiate glucagon-R mediated physiological responses.¹⁵⁶ The K_i values ranged from greater than 7,490 nM to greater than 23,600 nM, with the weakest binding affinity by Example peptides 1 and 2 (Phe²² or 1-Nal²² peptides lacking C-terminal Cys residues and PEGylation) as compared to Example peptides 3-5 (PEGylated C-terminal Cys residues).¹⁵⁷

99. Alsina-Fernandez reports results of an assay evaluating functional activation of hGIPR cells or hGLP-1R cells to generate intracellular cAMP that it

¹⁵⁴ EX1007 (Alsina-Fernandez), 13:12-15:3 & Table 2.

¹⁵⁵ EX1007 (Alsina-Fernandez), 15:1-3 & Table 2.

¹⁵⁶ EX1007 (Alsina-Fernandez), 15:4-16:25 & Table 3.

¹⁵⁷ EX1007 (Alsina-Fernandez), 16:22-23 & Table 3.

says demonstrate that all of Example peptides 1-5 bind and activate both GIPR and GLP-1R and can thereby initiate GIPR and GLP-1R-mediated physiological responses.¹⁵⁸ The Table 4 EC₅₀ values for GIPR were 0.005 nM and 0.023 nM for peptides 1 and 2 (1-Nal vs. Phe at position 22). Consistent with the K_i values, Table 4 reported the EC₅₀ of the PEGylated analogs was higher (0.207-0.277 nM) than that of the non-PEGylated analogs (0.005-0.023 nM). Similar K_i values, the lower the EC₅₀ value, the more potent the peptide compound for its intended effect. The same trends were observed for GLP-1, with Table 5 reporting EC₅₀ values of 0.036 nM and 0.045 nM for Example peptides 1 and 2 (non-PEGylated), but values ranging from 0.844-1.11 nM for the PEGylated analogues. Accordingly, the 1-Nal and Phe analogs achieved comparable efficacy in cell assays, while PEGylation reduced potency.

100. Alsina-Fernandez reports *in vivo* experiments in which administration of each of Example peptides 3-5 to obese mice and rats for fourteen days resulted in dose-dependent weight loss, fat mass loss, and reduced food intake as compared to vehicle.¹⁵⁹ Alsina-Fernandez also reports *in vivo* experiments in which administration of each of Example peptides 3-5 to obese mice or normal rats

¹⁵⁸ EX1007 (Alsina-Fernandez), 17:1-19:7 & Tables 4-5.

¹⁵⁹ EX1007 (Alsina-Fernandez), 19:8-20:9, 21:9-22:15 & Tables 6a-6b.

resulted in dose-dependent decreases in blood glucose as compared to vehicle.¹⁶⁰

Alsina-Fernandez also reports that administration of Example peptides 3 and 4 lowered the amounts of plasma lipid, including triglycerides and total cholesterol in obese rats as compared to vehicle-treated subjects.¹⁶¹

101. Alsina-Fernandez teaches treating diabetes and/or obesity by administering to a patient in need thereof an effective amount of a peptide of the invention.¹⁶² Alsina-Fernandez teaches formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient, including together with other therapeutic agents.¹⁶³ It teaches that the peptides are preferably formulated as pharmaceutical compositions administered by a variety of routes, and the such formulations and processes for preparing the same are well known in the art.¹⁶⁴ It further teaches administration in “dosages per week” that “fall within the range of 1 to 24 mg of peptide conjugate or 0.014 to 0.343 mg/Kg of body weight.”¹⁶⁵

B. WO 2010/011439 A1 (DiMarchi, et al.)

¹⁶⁰ EX1007 (Alsina-Fernandez), 20:10-21:8, 23:1-24:2 & Tables 7a-7b.

¹⁶¹ EX1007 (Alsina-Fernandez), 22:15-30.

¹⁶² EX1007 (Alsina-Fernandez), 3:32-4:14 (“method for inducing weight loss”), Claims 15-19.

¹⁶³ EX1007 (Alsina-Fernandez), 4:26-5:21, Claims 13-14.

¹⁶⁴ EX1007 (Alsina-Fernandez), 25:4-9.

¹⁶⁵ EX1007 (Alsina-Fernandez), 25:9-20.

102. International Publication No. WO 2010/011439, entitled “GIP-BASED MIXED AGONISTS FOR TREATMENT OF METABOLIC DISORDERS AND OBESITY” (“DiMarchi”) published on January 28, 2010, based on applications filed by Indiana University Research and Technology Corporation on June 16, 2009 (International Application No. PCT/US2009/047447), and February 10, 2009; August 20, 2008; July 3, 2008; and June 17, 2008 (respectively, U.S. Provisional Application Nos. 61/151,349; 61/090,448; 61/078,171; and 61/073,274). Accordingly, I have been advised that DiMarchi is prior art to the ’780 Patent.

103. DiMarchi relates to glucagon peptides that exhibit GIP agonist activity in addition to glucagon and/or GLP-1 activity.¹⁶⁶ DiMarchi teaches that pre-proglucagon is a 158 amino acid precursor polypeptide that is processed in different tissues to form a number of different proglucagon-derived peptides, including glucagon, glucagon-like peptide-I (GLP-1), glucagon-like peptide-2 (GLP-2) and oxyntomodulin (OXM).¹⁶⁷ DiMarchi also teaches that glucagon is a 29-amino acid peptide that corresponds to amino acids 33 through 61 of pre-proglucagon, while GLP-1 is produced as a 37-amino acid peptide that corresponds to amino acids 72 through 108 of pre-proglucagon, and GIP is a 42-amino acid

¹⁶⁶ EX1017 (DiMarchi), Abstract.

¹⁶⁷ EX1017 (DiMarchi), 1:13-21.

gastrointestinal regulator peptide that stimulates insulin secretion from pancreatic beta cells in the presence of glucose and is derived by proteolytic processing from a 133-amino acid precursor, pre-proGIP.¹⁶⁸ DiMarchi also notes that the Exendin-4 peptide shares about 50% amino acid identity with GLP-1, activates the GLP-1 receptor and, like GLP-1, has been shown to reduce hyperglycemia in diabetics.¹⁶⁹

104. DiMarchi provides glucagon peptides that exhibit activity at both the glucagon receptor and the GIP receptor (“glucagon/GIP co-agonists”); glucagon peptides that exhibit activity at the glucagon, GIP, and GLP-1 receptors (“glucagon/GIP/GLP-1 tri-agonists”); glucagon peptides that exhibit activity at the GLP-1 and GIP receptors, but in which the glucagon activity has been significantly reduced or destroyed (“GIP/GLP-1 co-agonists”); and glucagon peptides that exhibit activity at the GIP receptor, in which the glucagon and GLP-1 activity have been significantly reduced or destroyed (“GIP agonist glucagon peptides”).¹⁷⁰

105. For example, DiMarchi discloses that increased activity at the GLP-1 receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS or XGPSSGAPPPS to the C-terminus (i.e., Trp cage, C-terminal exenatide motif), and further increases in GLP-1 activity can be obtained by

¹⁶⁸ EX1017 (DiMarchi), 1:30-2:2.

¹⁶⁹ EX1017 (DiMarchi), 1:26-29.

¹⁷⁰ EX1017 (DiMarchi), 10:22-13:14.

modifying the GLP-1 amino acid at position 18, 28, or 29.¹⁷¹ In particular, DiMarchi reports that glucagon peptides having a glycine substitution for threonine at position 29 and the C-terminal extension of GPSSGAPPPS is four times as potent at the GLP-1 receptor as native glucagon modified to include the C-terminal extension.¹⁷² DiMarchi describes successfully creating and testing more than 260 exemplary GLP-1/GIP co-agonist peptides, of which the majority incorporated the GPSSGAPPPS exenatide C-terminal tail.¹⁷³

106. DiMarchi further teaches that the peptide compounds can be further modified to “[i]ncreas[e] solubility and/or duration of action or half-life in circulation and/or delaying the onset of action by acylation or alkylation of the glucagon peptide, as described herein.”¹⁷⁴ DiMarchi explains that the peptides can be acylated via a spacer¹⁷⁵, and that the acyl group can include fatty acids ranging from C4 to C30 fatty acids.¹⁷⁶

C. WO 2006/097537 A2 (Lau, et al.)

107. WO 2006/097537 A2 to Lau et al., entitled “ACYLATED GLP-1 COMPOUNDS” (“Lau”) published September 21, 2006, and claims priority to

¹⁷¹ EX1017 (DiMarchi), 5:7-11.

¹⁷² EX1017 (DiMarchi), 55:10-15.

¹⁷³ EX1017 (DiMarchi), Sequence Listing for SEQ ID NOS. 1-262.

¹⁷⁴ EX1017 (DiMarchi), 8:12-14.

¹⁷⁵ EX1017 (DiMarchi), 7:7-12.

¹⁷⁶ EX1017 (DiMarchi), 64:7-13

European Application No. 05102171 filed March 18, 2005. Accordingly, I have been advised that Lau is prior art to the '780 Patent.

108. Lau is directed to protracted duration of action and therapeutic uses of GLP-1 agonists.¹⁷⁷ It explains that a range of different approaches have been used to modify the structure of GLP-1 agonists to provide a longer duration of action *in vivo*, including introducing lipophilic substituents or acyl groups to an amino acid residue and attempting to associate the peptide with blood components, such as serum albumin in the patient, to extend *in vivo* half-life.¹⁷⁸ Because peptides are frequently administered as injections, which many patients find unpleasant, it explains, there was a need to develop GLP-1 agonists that can be administered less frequently than once daily, and preferably once weekly, while retaining an acceptable clinical profile.¹⁷⁹ Thus, Lau is specifically directed to GLP-1 peptides designed to provide once weekly administration.

109. To address that need, Lau teaches conjugating the lysine residue in position 20 (pro-peptide position 26) of GLP-1 to an albumin-binding moiety that increases the duration of action of the GLP-1 analogue.¹⁸⁰ Lau teaches that this approach to prolonging the action of the agonist is applicable not only to the

¹⁷⁷ EX1009 (Lau), Abstract.

¹⁷⁸ EX1009 (Lau), 1:10-24.

¹⁷⁹ EX1009 (Lau), 1:26-34.

¹⁸⁰ EX1009 (Lau), 2:1-5.

preferred GLP-1 analogues depicted therein, but also to other peptides with additional modifications to the amino acid sequence but which remain insulinotropic agents.¹⁸¹ Lau teaches this approach to protracted duration of action is useful because the acylated GLP-1 analogues can bind to albumin and the GLP-1 receptor simultaneously, such that they retain adequate affinity for the receptor.¹⁸²

110. Among the specific design choices taught by Lau include modifying at least one non-proteinogenic amino acids at positions 7 and/or 8 relative to the GLP-1 sequence. Another specific design choice taught by Lau is the acylation of the lysine residue at GLP-1 position 20 (26 in the pro-peptide).

111. Accordingly, Lau teaches the structure of the compound identified as once-weekly semaglutide, including the structure of the albumin-binding moiety conjugated to the epsilon-amino of the lysine at position 20 (26 in the pro-peptide) in Example 4 (containing 16 methylene units, and 18 total carbon atoms (i.e., C18) in the fatty diacid chain), as well as a homologue (with 18 methylene units and 20 total carbon atoms (i.e., C20) in the fatty diacid chain) in Example 5.¹⁸³

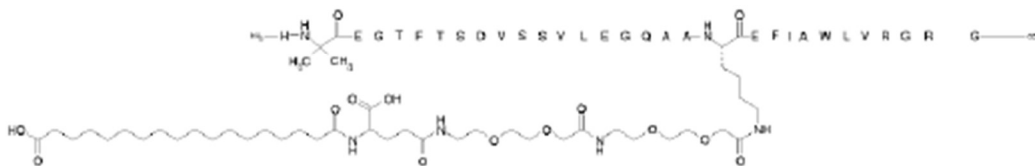
¹⁸¹ EX1009 (Lau), 3:8-4:8.

¹⁸² EX1009 (Lau), 6:6-21.

¹⁸³ EX1009 (Lau), 47:4-22 (Example 4), 47:23-48:12 (Example 5); *see also* EX1009 (Lau), 17:1-10.

Example 4

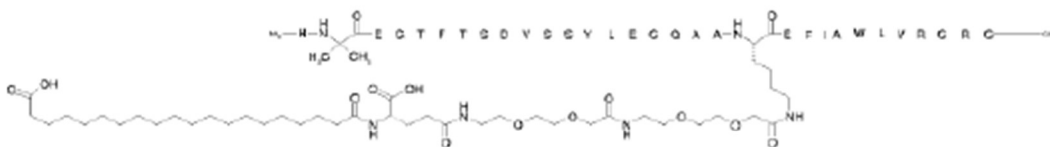
- 5 N-ε²⁶-[2-(2-[2-(2-[2-(4-(17-Carboxyheptadecanoylamino)-4(S)-
carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-
37)peptide.



- [Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide
10 synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was

Example 5

- 25 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-
carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-
37)peptide.



IX. GROUND 1. CLAIMS 1-2, 4-7, 9-10, 12-18 ARE OBVIOUS OVER ALSINA-FERNANDEZ IN VIEW OF DiMARCHI AND LAU

112. It is my opinion that the prior art, including Alsina-Fernandez in view of DiMarchi and Lau, renders obvious the development of peptides that fall within the scope of claims 1-2, 4-7, 9-10, and 12-18 of the '780 Patent, as summarized in the table below:

Ground	Reference(s)	Basis	Claims Challenged
1	Alsina-Fernandez (EX1007) in view of DiMarchi (EX1017) and Lau (EX1009)	35 U.S.C. § 103(a)	1-2, 4-7, 9-10, and 12-18

113. As I have outlined in my analysis, based on the understanding in the field prior to 2015, a POSA was motivated to develop GLP-1/GIP co-agonist compounds for the treatment of diabetes mellitus, as well as weight loss, as the dosing of GLP-1 agonist compounds was limited by the nausea and vomiting associated with these compounds, preventing these compounds from reaching their full efficacy for glycemic control and weight loss. The prior art provided guidance in the form of well-known structural substitutions and modifications that represented rational design strategies related to the development of co-agonists of GIP/GLP-1, particularly in view of a POSA's well-established motivations (1) solve/mitigate the issues associated with nausea and vomiting caused by GLP-1 agonist compounds; (2) minimize any potential immunogenicity associated with regular administration of the GLP-1/GIP co-agonist compounds; and (3) provide for a longer half-life and duration of effect, allowing for less frequent injections of the medication (e.g., once-weekly dosing), as compared to the dosing frequency required with shorter half-life compound (e.g., once daily dosing).

114. Additionally, it is my understanding that secondary considerations of non-obviousness (e.g., surprising and unexpected results associated with the claimed compounds) may provide additional factors that may weigh against a finding of obviousness. However, as previously outlined, I have reviewed the specification of the '780 Patent, and it is my opinion that there is no evidence of

surprising and unexpected results, or any other secondary considerations, that would overcome the obviousness of the claimed peptides, compositions, and methods, based on the combined teachings of Alsina-Fernandez in view of DiMarchi and Lau.

115. My opinions are discussed in more detail in the sections set forth below.

A. Claim 1

116. It is my opinion that claim 1 of the '780 Patent is obvious over Alsina-Fernandez in view of DiMarchi and Lau. For reference, the language of claim 1 is provided below:

1. A compound of Formula:

$\text{YX}_1\text{EGTFTSDYSIX}_2\text{LDKIAQKAX}_3\text{VQWLIAGGPSSGAPPPS};$

wherein

X_1 is Aib;

X_2 is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_a-CO—(CH₂)_b—CO₂H wherein a is 1 to 2 and b is 10 to 20;

X_3 is Phe or 1-Nal;

and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),

or a pharmaceutically acceptable salt thereof.

1. Known Problems with GLP-1 Compounds Prior to 2015, and A Promising Prior Art GIP/GLP-1 Co-Agonist

117. By January 2015, it was well known in the art that GLP-1 agonist compounds and products were being used and developed for not only the treatment of type 2 diabetes mellitus (T2D), but also for weight loss. Specifically, by December 2014, liraglutide (a GLP-1 receptor agonist) had been approved by the FDA for both the treatment of diabetes (as the Victoza[®] product) and for chronic weight management (as the Saxenda[®] product).¹⁸⁴ Indeed, it was well established that obesity had become a serious public health issue due to its prevalence and common association with high rates of morbidity and mortality, driving significant interest in the development of treatments specific to obesity beyond known measures at the time, such as bariatric surgery.¹⁸⁵ And the field had also begun to recognize GLP-1 receptor agonists as a new and promising treatment option for obesity.¹⁸⁶ But, it was also known in the field that the nausea and vomiting associated with GLP-1 agonists limited use of the compounds.¹⁸⁷ Indeed, by the '780 Patent's own admission, "[d]osing of GLP-1 analogues has been found to be

¹⁸⁴ See, e.g., EX1050 ("VICTOZA"), EX1013 ("SAXENDA").

¹⁸⁵ See EX1083 (Torekov).

¹⁸⁶ EX1083 (Torekov), abstract ("with the GLP-1 analogues combining a moderate weight loss with beneficial effects on metabolic and cardiovascular risk factors, it seems that we are on the right track for future treatment of obesity.").

¹⁸⁷ See, e.g., EX1061 (Finan), 11-12 (discussing "dose-limiting nausea complications that restrict current selective GLP-1R agonists.").

limited by adverse effects, such as **nausea and vomiting**, and as a consequence dosing most often cannot reach full potential efficacy for glycemic control and weight loss.”¹⁸⁸ With this known problem in mind, a POSA would have looked for strategies to solve or mitigate the nausea issue.

118. Finan, published in 2013, establishes that co-agonists of GLP-1 and GIP can enhance weight loss efficacy, while at the same time lessening nausea, stating:

GLP-1 agonist therapy provides modest weight loss well below what is needed for sizeable metabolic improvements and often is accompanied by dose-limiting, adverse gastrointestinal events. Here, we show that a balanced, unimolecular combination of GLP-1R and GIPR agonism provides greater metabolic efficacy than selective monoagonism in different species from rodents to primates and humans, *without apparent gastrointestinal discomfort*.¹⁸⁹

119. Finan explains that co-agonists of GLP-1 and GIP provide greater metabolic efficacy than selective GLP-1 agonists, but without the gastrointestinal discomfort (e.g., nausea and vomiting) associated with selective GLP-1 agonists. Finan further explains that the addition of GIP agonism enhances GLP-1 efficacy, stating:

Collectively, the results indicate the potential for using GIP as an additional element to enhance the pharmacology of selective GLP-1R agonists by strengthening the

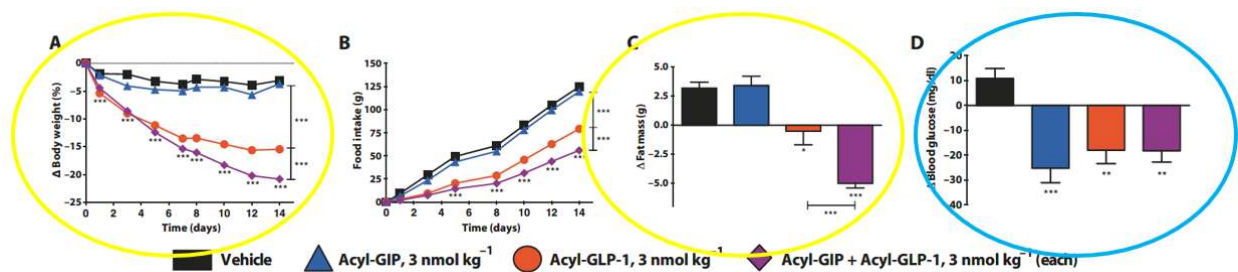
¹⁸⁸ EX1001 ('780 Patent), 1:37-40 (emphasis added).

¹⁸⁹ EX1061 (Finan), 11-12. (Internal citations omitted) (Emphasis added).

inherent efficacy and broadening the therapeutic index. We believe that the combination of the enhanced efficacy and therapeutic index confers lower drug exposure as a consequence of lower constitutive receptor occupancy levels, thus closely resembling a physiological setting and *circumventing the dose-limiting nausea complications that restrict current selective GLP-1R agonists*. These clinical results support increases in dose to further enhance metabolic control and maximize weight loss....¹⁹⁰

120. Finan explains that the addition of GIP agonism to GLP-1 agonists strengthens the inherent efficacy and therapeutic index of GLP-1 agonists, meaning results can be achieved using lower doses (more closely approximating physiologic levels), and circumventing the dose-limiting nausea complications typically associated with GLP-1 agonists.

121. As shown in the annotated version of Finan's Figure 3 below, co-GLP-1/GIP agonism provided enhanced weight and fat loss (yellow circles), while maintaining blood glucose lowering efficacy similar to a GLP-1 agonist (blue circle) in diet-induced obese (DIO) mice.¹⁹¹



¹⁹⁰ EX1061 (Finan), 12.

¹⁹¹ EX1061 (Finan), 3, Fig. 1A-1D.

122. Consequently, based on the disclosure of Finan, as of 2013, a POSA would have been motivated to investigate co-GLP-1/GIP agonist compounds as an alternative to selective GLP-1 receptor agonists, as co-GLP-1/GIP agonist compounds were shown to maintain, and in some instances enhance, the glycemic control and weight loss properties of GLP-1 compounds, while circumventing the nausea typically associated with GLP-1 administration.

123. In view of this motivation, a POSA would have looked to Alsina-Fernandez as a primary source of guidance, as Alsina-Fernandez discloses a GIP/GLP-1 co-agonist peptide sequences useful for treating diabetes and/or reducing body weight.¹⁹² Alsina-Fernandez discloses that its GIP/GLP-1 co-agonist peptide sequence is both potent and efficacious for reducing body weight and reducing glucose sensitivity, explaining that dual agonism uses the glucose-lowering effects of GLP-1 to better harness the insulin-secretion effects of GIP.¹⁹³ Thus, Alsina-Fernandez provides teachings regarding co-GLP-1/GIP agonists, and in fact notes that the co-agonists described therein address some of the very same issues that Finan discusses and attempts to address:

The present invention provides new potent and efficacious peptides with amino acid substitutions introduced to

¹⁹² EX1007 (Alsina-Fernandez), Abstract, 2:12-25, 5:24-27, Claims 1-12.

¹⁹³ EX1007 (Alsina-Fernandez), 2:5-10, 11:20-27, 1:8-21.

modulate activity for both GIP and GLP-1 while maintaining selectivity over glucagon. This invention achieves the glucose-lowering effects of GLP-1 and harness the glucose-stimulated insulin secretion effects of GIP. Moreover, certain compounds of the invention provide effective treatments to reduce body weight.¹⁹⁴

124. In view of these teachings, a POSA would have looked at Alsina-Fernandez as a lead reference in the development of a co-GLP-1/GIP agonist. Based on the disclosure of Alsina-Fernandez, a POSA had good reason to make and evaluate structurally similar peptide sequences likely to share the GIP/GLP-1 receptor co-agonist functionality. In particular, a POSA was motivated to look to Alsina-Fernandez as the lead publication, and the compound of Example 2 of Alsina-Fernandez, as a lead compound for further development and optimization because of its most promising GIP/GLP-1 dual agonism properties. Alsina-Fernandez focuses on a primary amino acid sequence with three variable amino acids (noted as Xaa¹⁻³):

The present invention provides a peptide comprising the sequence:

¹⁹⁴ EX1007 (Alsina-Fernandez), 2:5-10.

wherein Xaa¹ at position 22 is Nal or Phe; Xaa² at position 43 is Cys or absent; Xaa³ at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa² at position 43 or Xaa³ at position 44 is Cys, then either or both are optionally pegylated.¹⁹⁵

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-R-A-Xaa¹-V-Q-W-L-I-A-Aib-K-G-K-K-Q-E-W-K-H-Q-I-T-Q-Xaa²-Xaa³

Xaa³= cysteine (Cys or “C”) or absent

¹⁹⁵ EX1007 (Alsina-Fernandez), 2:12-25.

position 22 is Phe (F) or 1-Nal.¹⁹⁶ Specifically, the K_i values reported in Tables 1 and 2 represent receptor binding affinities, and correlate to the IC_{50} concentration for agonist activity of the GIP and GLP-1 receptors, respectively, reflecting the concentration of the compound required to provide agonist activity at 50% of the receptors. The lower the K_i value, the more potent the binding to the GIP and GLP-1 receptors. Consequently, a POSA would look to the values in Tables 1 and 2 for the compounds with the lowest K_i values, as that would be indicative of the most potent binding/agonist activity at the GIP and GLP-1 receptors.

127. I have provided below annotated versions of Tables 1 and 2 of Alsina-Fernandez.¹⁹⁷

GIP Receptor (GIP-R) Binding Affinities Reported in Table 1:

Table 1

Example	K_i
1	0.044 nM
2	0.023 nM
3	9.79 nM
4	8.23 nM
5	9.22 nM

GLP-1 Receptor (GLP-1-R) Binding Affinities Reported in Table 2:

¹⁹⁶ EX1007 (Alsina-Fernandez), 11:29-15:4.

¹⁹⁷ EX1007 (Alsina-Fernandez), 13:6-9, 14:32-15:3.

Table 2

Example	Ki
1	0.096 nM
2	0.059 nM
3	9.00 nM
4	5.27 nM
5	6.20 nM

128. As I have highlighted in Table 1 and Table 2 above, the compound of Example 2 demonstrated the lowest Ki value for both the GIP receptor binding (Table 1) and GLP-1 receptor binding (Table 2). Consequently, a POSA would know that the compound of Example 2 provides the most potent binding of the GIP and GLP-1 receptors.

129. Additionally, Alsina-Fernandez also reports Ki values for binding to the glucagon receptor (Gluc-R) in Table 3.¹⁹⁸ In the context of co-GIP/GLP-1 agonists that are designed to provide glycemic control (e.g., by lowering blood sugar concentration), binding to the glucagon receptor is considered undesirable, as Alsina-Fernandez explains that glucagon receptor binding triggers increased blood glucose levels, and “is undesirable in a diabetic setting.”¹⁹⁹ Thus, a POSA understands that a higher Ki value (lower binding affinity) for the glucagon

¹⁹⁸ EX1007 (Alsina-Fernandez), 16:22-24.

¹⁹⁹ EX1007 (Alsina-Fernandez), 1:16-17.

receptor would be desirable, as that would minimize the release of blood glucose associated with stimulation of the glucagon receptor.

130. I have provided below an annotated version of Table 3 of Alsina-Fernandez.²⁰⁰

Glucagon Receptor (Gluc-R) Binding Affinities Reported in Table 3

Table 3

Example	Ki
1	> 23,600 nM
2	> 23,600 nM
3	>7,890 nM
4	>7,490 nM
5	>7,490 nM

131. As I have highlighted in Table 3 above, the compound of Example 2 demonstrated the highest Ki value (along with the compound of Example 1) for glucagon receptor binding affinity, representing the weakest affinity for the glucagon receptor. Consequently, a POSA would have known that the compound of Example 2 represents the weakest binding of the glucagon receptor, which was preferred, as binding to the glucagon receptor was undesirable (due to increased blood glucose levels triggered by stimulation of the glucagon receptor).

²⁰⁰ EX1007 (Alsina-Fernandez), 16:22-24.

132. Based on the data reported in the Examples, particularly in Tables 1-3, Alsina-Fernandez teaches that the compound of Example 2 had the most potent binding affinity for the GIP and GLP-1 receptors, and the weakest binding affinity for the glucagon receptor. Additionally, while Example 1 demonstrated a binding affinity for GIP and GLP-1 that was better than Examples 3-5, the GIP and GLP-1 receptor binding affinities for Example 2 were better (0.023 nM GIP receptor K_i for Example 2 vs. 0.044 nM GIP receptor K_i for Example 1; 0.059 nM GLP-1 receptor K_i for Example 2 vs. 0.096 nM GLP-1 receptor K_i for Example 1). It is also well-known that 1-Nal (naphthylalanine, the amino acid present at position 22 of Example 1) is a non-natural amino acid with a large aromatic side chain (i.e., naphthalene), markedly increasing the potential for immunogenicity against the peptide of Example 1. The combination of these factors would have led a POSA to focus on the compound of Example 2 as the lead candidate for a co-GIP/GLP-1 agonist for further development and research.

133. The amino acid sequence of the peptide of Example 2 of Alsina-Fernandez is provided below:

EXAMPLE 2

```

Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
      5                      10
Asp-Lys-Ile-Ala-Gln-Arg-Ala-Phe-Val-Gln-Trp-Leu-Ile-Ala-
15                      20                      25
Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln
      30                      35                      40
(SEQ ID NO: 5)

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134. As can be seen above, the compound of Example 2 includes Phe (“F”) at position 22, and Xaa² and Xaa³ are absent. For ease of viewing, I have provided the sequence of Example 2 in linear form below, with the Phe residue at position 22 highlighted:

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-R-A-F-V-Q-W-L-I-A-Aib-K-G-K-K-Q-E-W-K-H-Q-I-T-Q
5 10 15 20 25 30 35

135. Further, I note that Alsina-Fernandez also reports that the compounds may include Cys residues at positions 43 and 44, and the compounds may also be PEGylated at the Cys43 and Cys44 residues.²⁰² However, as noted in Tables 1-3 above, the compounds with PEGylated Cys residues at positions 43 and 44 (i.e., the compounds of Examples 3, 4, and 5) had lower binding affinities for the GIP and GLP-1 receptors (an ~100-400 fold lower binding affinity, depending on the peptide),²⁰³ and a higher binding affinity for the glucagon receptor, as compared to

²⁰¹ EX1007 (Alsina-Fernandez), 8:15-22.

²⁰² EX1007 (Alsina-Fernandez), 2:12-25.

²⁰³ EX1007 (Alsina-Fernandez), 13:6-9, 14:32-15:3.

the compound of Example 2 (~3-fold higher binding affinity).²⁰⁴ This additional data would further motivate a POSA to focus on the compound of Example 2 as the lead candidate.

136. In addition to these PEGylated compounds providing less advantageous binding affinities for the GIP and GLP-1 receptors (*see* Table 1 and Table 2, respectively) and glucagon receptor (*see* Table 3), a POSA was motivated to avoid PEGylated compounds based on the risk of potential immunogenicity. Specifically, Alsina-Fernandez was filed in March 2011 (claiming priority to US Prov. Pat. App. No. 61/317,850 filed March 26, 2010). Subsequently, in 2012, Garay et al. reported that, in contrast to the common thinking that PEG is non-immunogenic and non-antigenic (as was generally the thinking in the art at the time Alsina-Fernandez was filed), up to 25% of healthy blood donors (*i.e.* donors with no indication of ever being previously treated with a PEGylated drug), and up to 89% of patients treated with PEGylated drug, were shown to have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds.²⁰⁵ The response elicited by these PEG antibodies can result in decreased therapeutic efficacy and reduced tolerance to PEGylated drug compounds.²⁰⁶ Further, the

²⁰⁴ EX1007 (Alsina-Fernandez), 16:22-24.

²⁰⁵ EX1022 (Garay), Abstract, 1320.

²⁰⁶ EX1022 (Garay), Abstract, 1320.

desire to avoid potential immunogenicity was particularly strong for compounds intended to be administered chronically and with repeated dosing (e.g., weekly), as opposed to acute, single, or infrequent administration, where some immunogenicity might be acceptable to treat an acute condition, and the peptide is only administered a small number of times. Patients receiving the GIP/GLP-1 co-agonist would likely expect to be taking the compound regularly for long periods of time (perhaps the rest of their life).

137. Consequently, even though Alsina-Fernandez discussed the use of PEGylated peptide compounds in Examples 3, 4, and 5, the risk of potential immunogenicity associated with the PEG further motivated a POSA to focus on the peptide of Example 2, which nonetheless provided the most desirable binding profile for the GIP, GLP-1, and glucagon receptors.

138. Based on the disclosures of Alsina-Fernandez, a POSA would have looked to the peptide of Example 2 as a lead compound for further development and optimization because of its most promising GIP/GLP-1 co-agonist properties (and high degree of selectivity over the glucagon receptor) and the likelihood that this compound would be favorably improved through further modification.

2. *Exenatide C-Terminal Motif Useful for GIP/GLP-1 Co-Agonists*

139. In view of the teachings of Alsina-Fernandez, a POSA would have been motivated to look for guidance on strategies to improve the efficacy of the co-

GIP/GLP-1 agonists described in Alsina-Fernandez. In this regard, Alsina-Fernandez itself cites one reference, WO 2010/011439, as previously describing co-GIP/GLP-1 agonists:

Certain GIP analogs have been described in WO 2010/016940 and WO 2010/016944. ***Certain glucagon analogs have been described as exhibiting both GIP and GLP-1 activity in WO 2010/011439.***²⁰⁷

Consequently, based on this statement in Alsina-Fernandez, a POSA would have looked to WO 2010/011439 for additional guidance on co-GIP/GLP-1 agonist compounds and strategies. WO 2010/011439 is the DiMarchi reference I previously summarized, and which I am relying on as part of the combination of prior art rendering obvious the '780 Patent claims.

140. DiMarchi teaches strategies for enhancing GIP and/or GLP-1 receptor activity. Significantly, DiMarchi discloses that the incorporation of a glycine (G) at position 29 and attachment of the GPSSGAPPPS tail to the glycine residue at position 29 enhances GLP-1 receptor potency, stating:

Increased activity at the GLP-I receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS (SEQ ID NO: 95) or XGPSSGAPPPS (SEQ ID NO: 96) to the C-terminus. GLP-I activity in such analogs can be further increased by modifying the amino acid at position 18, 28 or 29, or at position 18 and 29, as described herein.²⁰⁸

²⁰⁷ EX1007 (Alsina-Fernandez), 1:27-29. (Emphasis added).

²⁰⁸ EX1017 (DiMarchi), 5:7-11.

...

In some embodiments, e.g., in glucagon peptides which comprise the C-terminal extension, the threonine at position 29 of the native glucagon peptide is replaced with a glycine. For example, a glucagon peptide having a glycine substitution for threonine at position 29 and comprising the C-terminal extension of GPSSGAPPPS (SEQ ID NO: 95) is *four times* as potent at the GLP-I receptor as native glucagon modified to comprise the same C-terminal extension.²⁰⁹

141. DiMarchi established that adding an extension peptide such as GPSSGAPPPS (SEQ ID NO: 95) or XGPSSGAPPPS (SEQ ID NO: 96) to the C-terminus enhances GLP-1 activity. DiMarchi also provides specific guidance that incorporating a glycine (G) residue at position 29, and connecting the GPSSGAPPPS tail to the glycine at position 29 resulted in *four times* the GLP-1 receptor binding potency, as compared to attaching the GPSSGAPPPS extension to the threonine present in the native glucagon peptide.

142. Additionally, as discussed previously,^{210,211} the GGPSSGAPPPS motif had been successfully appended to DPP-IV-resistant GLP-1 to improve its potency and metabolic stability without inducing undue immunogenicity. The C-terminal motif GGPSSGAPPPS found in the FDA-approved GLP-1 receptor agonist exenatide was associated with reduced clearance, improvement in half-life,

²⁰⁹ *Id.* at 55:10-17. (Emphasis added).

²¹⁰ EX1070 (Fineman), Abstract.

²¹¹ EX1071 (Buse), 1700-1701, Abstract.

and less susceptibility to undesirable DPP-IV cleavage, as demonstrated by a prolonged half-life of 2.4 hours.²¹² The C-terminal motif GGPSSGAPPPS in exenatide also did not trigger strong or adverse immunogenicity, as evidenced by the low titer anti-exenatide antibodies reported for Byetta[®] and Bydureon[®].²¹³

143. Additionally, a POSA would have recognized that the compound of Example 2 of Alsina-Fernandez, unnecessarily employs a non-natural Aib residue at position 29, and also employs a long C-terminal motif that does not appear in any of the natural ligands or the FDA-approved therapeutic ligands. It is well-established that the inclusion of non-natural amino acids increased the likelihood of immunogenicity. Consequently, a POSA would have been motivated to replace the unnatural C-terminal residues 29-39 of the Example 2 compound of Alsina-Fernandez with exenatide's natural C-terminal GGPSSGAPPPS²¹⁴ motif. A POSA would have recognized that this prior art substitution would avoid unnecessary use of the non-natural (and potentially immunogenicity-inducing) Aib at position 29 by

²¹² EX1054 (Byetta), 3 (reporting a terminal half-life of exenatide of 2.4 hours); EX1076 at 4013 (“GLP-1 has a very short half-life of ~2 min”).

²¹³ *See, e.g.*, EX1053 (“BYDUREON”), 9 (“...452 BYDUREON-treated patients (49%) had low titer antibodies (≤ 125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers.”); EX1054, 14 (“In the 30-week controlled trials 38% of patients had low titer anti-exenatide antibodies at 30 weeks. For this group, the level of glycemic control (HbA1c) was generally comparable to that observed in those without antibody titers.”).

²¹⁴ *See, e.g.*, EX1053 (“BYDUREON”), 9.

employing the Gly found naturally in endogenous and synthetic FDA-approved GLP-1 receptor agonists exenatide and liraglutide, as Gly at position 29 was known to elicit low-titer anti-drug antibodies consistent with therapeutic efficacy.²¹⁵

144. A POSA would have expected that Gly was less immunogenic than the non-natural Aib residue and that exenatide's natural C-terminal motif contributed to peptide stability against proteases.²¹⁶ Accordingly, a POSA would have reasonably expected reduced immunogenicity²¹⁷ as compared to the sequence of the Example 2 compound of Alsina-Fernandez, which would have provided a POSA with an additional reason to apply the prior art exenatide C-terminal motif to the co-GIP/GLP-1 agonist disclosed in Alsina-Fernandez.²¹⁸

²¹⁵ EX1009 (Lau), 61:1-62:37, (Example 4, providing endogenous sequence for 31-residue version of GLP-1 with G at position 29), 3:25-28 (defining GLP-1), 4:4-16 (invoking 39-residue sequence of Exendin-4); EX1053 ("BYDUREON"), 9 ("...452 BYDUREON-treated patients (49%) had low titer antibodies (≤ 125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers."); EX1054, 1-2, 14 (exenatide sequence and favorable safety profile, "In the 30-week controlled trials 38% of patients had low titer anti-exenatide antibodies at 30 weeks. For this group, the level of glycemic control (HbA1c) was generally comparable to that observed in those without antibody titers."); EX1070, Abstract (exenatide safety) EX1071, Abstract, 1700-1701 (low frequency and magnitude antibody formation for liraglutide).

²¹⁶ See Section VII.B.-C. above.

²¹⁷ EX1053 ("BYDUREON"), 9; EX1054 ("BYETTA"), 14.

²¹⁸ Alsina-Fernandez recognized the goal of avoiding undesirable protease cleavage. It references its use of Aib residues at position 2 and 13, which substitutions were known to prevent DPP-IV-catalyzed and activity-defeating peptide cleavage, Alsina-Fernandez teaches SEQ ID NO:1 is less susceptible to rapid metabolic deactivation by DPP-IV. EX1007 (Alsina-

145. DiMarchi discloses more than 260 exemplary peptide sequences, of which more than 160 incorporated the GPSSGAPPPS tail, as described in the specification of DiMarchi, so this was clearly a preferred/prominent design strategy in DiMarchi.²¹⁹ Further, DiMarchi states that “[e]nhanced activity at the GLP-1 receptor is provided by replacing the carboxylic acid of the C-terminal amino acid with a charge-neutral group, such as an amide or ester,”²²⁰ suggesting to a POSA that the terminal -NH₂ amide group attached to the terminal serine would further enhance GLP-1 receptor activity. Indeed, Finan, which published in 2013, several years after both Alsina-Fernandez (filed in 2011) and DiMarchi (filed in 2009), includes a number of exemplary peptides, the majority of which include the GPSSGAPPPS-NH₂ exenatide C-terminal tail, suggesting this was a continuing design strategy/motivation in the years following Alsina-Fernandez and DiMarchi.²²¹ Researchers in this field would have been keenly aware of such peptide designs leading up to the filing of the ’780 Patent in 2015.²²²

Fernandez), 5:22-23. C-terminal substitution of residues 29-39 with exenatide’s C-terminal GGPSSGAPPPS motif is thus not only consistent with the scientific purposes disclosed in DiMarchi, but also is consistent with the scientific goals of Alsina-Fernandez.

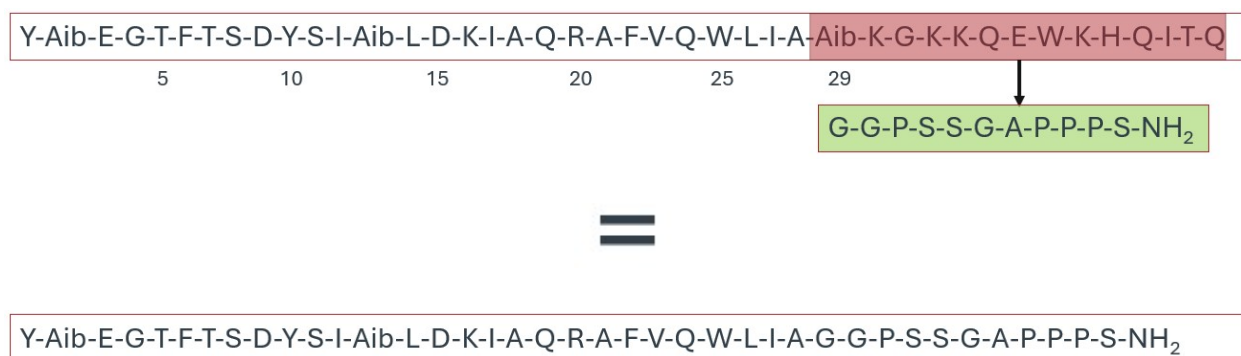
²¹⁹ EX1017 (DiMarchi), Sequence Listing for SEQ ID NOS. 1-262.

²²⁰ EX1017 (DiMarchi), 33:20-21.

²²¹ EX1061 (Finan), Supplemental Figure 1.

²²² It is also noted that the ’780 Patent shares two overlapping inventors with Alsina-Fernandez – Bovkist and Alsina-Fernandez. Still further, the first named inventor on DiMarchi (i.e., DiMarchi), “is a former Group Vice President at Eli Lilly and later at Novo Nordisk.” *See* www.chem.indiana.edu/faculty/richard-dimarchi/. Eli Lilly and Company is the named applicant

146. Based on all of these factors, it is my opinion that a POSA would have been motivated to replace the unnatural C-terminal residues 29-39 of the Example 2 compound of Alsina-Fernandez with exenatide's natural C-terminal GGPSSGAPPPS motif and terminal amide group (-NH₂) taught by DiMarchi. Given the prominence of the use of the C-terminal GPSSGAPPPS tail across numerous different peptides in DiMarchi, as well as the majority of the exemplary peptides in Finan, a POSA would have reasonably expected that the C-terminal GPSSGAPPPS motif could be successfully utilized in the peptide of Example 2 of Alsina-Fernandez as well. In doing so, a POSA would reasonably expect that the exenatide tail would not only enhance the GLP-1 receptor binding activity of the peptide, but would also help to minimize immunogenicity. Applying the exenatide tail to the Example 2 peptide of Alsina-Fernandez yields the following:



on the '780 Patent and Alsina-Fernandez, and Novo Nordisk is the named applicant on Lau (discussed below).

3. Albumin-Binding Substituents to Prolong the Duration of Action and Dosing Frequency

147. While Alsina-Fernandez and DiMarchi provide guidance for developing a co-GIP/GLP-1 agonist and provide rational design strategies for (1) enhancing binding affinity/potency for GIP and GLP-1 receptors, while (2) providing lower binding affinity at the glucagon receptor, providing the desired selectivity, neither publication addresses the dosing frequency.

148. A POSA was well-aware that the GIP/GLP-1 agonist peptides described in Alsina-Fernandez and DiMarchi (as well as the peptide sequence formed from the combination of the teachings of the two references) would need to be administered via injection. Both Alsina-Fernandez and DiMarchi reference injecting the peptide formulations,²²³ and it was well-known in the art that other GLP-1 agonist compounds were administered as injections.²²⁴ It was also known that these compounds had a short half-life, meaning the compound would require regular administration to maintain therapeutic drug levels in the body—likely requiring daily injections.²²⁵

²²³ EX1007 (Alsina-Fernandez), 25:4-6 (“Most preferably, such compounds are for parenteral administration”); EX1017 (DiMarchi), 90:27-29 (“The compounds of the present invention can be used in some embodiments to prepare pre-formulated solutions ready for injection.”).

²²⁴ See, e.g., EX1054 (“BYETTA”) (twice daily exenatide injection); EX1013 (“SAXENDA”) (once daily liraglutide injection); EX1050 (“VICTOZA”) (once daily liraglutide injection).

²²⁵ See, e.g., EX1054 (“BYETTA”), 3 (reporting a half-life of 2.4 hours); EX1013 (“SAXENDA”), 14-15 (reporting that liraglutide has a half-life of 13 hours, suitable for once-

149. Additionally, it was also well-known that many patients have “needle-phobia” and prefer medications with as few injections as possible – if injections are required, it would be preferred to have injections every several days, or once every week would be highly preferred.²²⁶

150. While half-life values are not reported for the peptides in Alsina-Fernandez, a POSA would not expect that these peptides would support prolonged dosing (e.g., once-weekly dosing, or even dosing less than once per day). Example 2 of Alsina-Fernandez does not include an albumin-binding moiety, which, as I discussed previously in relation to semaglutide, was known prior to 2015 to significantly prolong half-life (in the case of semaglutide, resulting in a ~160-hour half-life). Additionally, even the PEGylated peptides of Alsina-Fernandez (which a POSA would know to have longer half-lives because of their PEGylation) were still administered every three days when they were assessed *in vivo*.²²⁷ Further, while the incorporation of the C-terminal exendin tail would be expected to prolong the half-life of the Example 2 peptide of Alsina-Fernandez (similar to what was achieved with exenatide, providing a half-life of ~2.4 hours), this prolonging would be limited to improved stability against proteolysis, and would not be

daily administration); EX1050 (“VICTOZA”), 12 (reporting that liraglutide has a 13-hour half-life).

²²⁶ EX1009 (Lau), 1:26-33.

²²⁷ EX1007 (Alsina-Fernandez), at 19:18-20.

expected to approach anything close to that required to provide once-weekly (or even less frequent than once daily), as evidenced by the fact that Byetta[®] (exenatide) was still required to be administered once daily. A major contributing factor is that, without binding to larger proteins (e.g., serum albumin), small peptides (such as Example 2 in Alsina-Fernandez and exenatide) are readily filtered from the bloodstream by the kidneys. Consequently, in addition to enhancing the GIP/GLP-1 receptor potency (while minimizing glucagon receptor binding affinity), and also minimizing the potential for immunogenicity, a POSA was further motivated to address how to extend the half-life of the co-GIP/GLP-1 agonist formed from the combination of Alsina-Fernandez and DiMarchi to allow for extended dosing frequency (e.g., once weekly dosing).

151. By 2013, researchers had begun to explore peptide design strategies to prolong the half-life and dosing frequency of GLP-1 compounds. Lorenz discusses this approach with respect to GLP-1 analogs semaglutide and liraglutide, stating:

GLP-1 agonists on the market and in clinical development. Therapeutic utility of natural GLP-1 is limited by its rapid degradation by serum proteases, predominantly dipeptidyl peptidase IV (DPP-IV), but also other enzymes such as neutral endopeptidases (NEP), plasma kallikrein or plasmin. Therefore, GLP-1 has a very short half-life of ~2 min following intravenous administration. A variety of strategies have been applied to provide novel GLP-1 RAs

with longer-term in vivo activity following subcutaneous administration, which are described below.²²⁸

...

Fatty acid conjugation. The concept of fatty acid conjugation is a well established strategy to prolong the action of peptides by facilitating binding to serum albumin thereby reducing their renal clearance. Landmark achievements in this area have been the development of long active insulin analogs.

...

Semaglutide. Semaglutide is a next generation GLP-1 analog from Novo Nordisk, currently in phase 3 clinical development for T2DM as a once weekly injection. Semaglutide's structure is based on liraglutide, with two further modifications: Gly in position 8 is replaced by Aib, a beneficial modification already applied in taspoglutide. Furthermore, the fatty acid side chain has been modified towards a N6-[N-(17-carboxy-1-oxoheptadecyl-L- γ -glutamyl[2-(2-aminoethoxy)ethoxy]acetyl[2-(2-aminoethoxy)ethoxy]acetyl] residue (see Fig. 2a). ***The human half-life is ~160 h.*** In a 12 week phase 2 trial in T2DM patients, semaglutide was tested at 5 doses (0.1-1.6 mg) once-weekly. Semaglutide ≥ 0.2 mg dose dependently reduced HbA1c from baseline up to 1.7% (vs 0.5% reduction for placebo) and for doses ≥ 0.8 mg also body weight by up to 4.8 kg (vs 1.2 kg for placebo).²²⁹

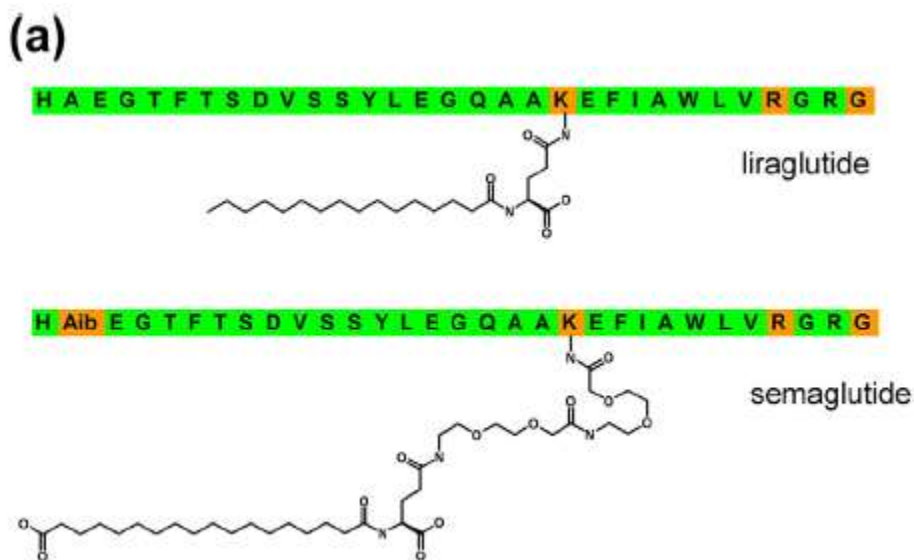
152. Lorenz established the understanding in the art prior to 2015 that semaglutide was a “next-generation GLP-1 analog” with a ~160-hour half-life (allowing for once weekly administration), and that semaglutide demonstrated

²²⁸ EX1076 (Lorenz), 4013.

²²⁹ EX1076 (Lorenz), 4014. (Emphasis added).

efficacy in both the treatment of Type 2 Diabetes Mellitus (as evidenced by reduction in HbA1c) and in providing weight-loss (4.8 kg weight reduction), even when administered once weekly.²³⁰

153. Additionally, as referenced in the passage above, Lorenz provides Fig. 2a, illustrating the fatty acid side chain modification utilized by semaglutide:²³¹



154. As illustrated in Fig. 2(a) above, Lorenz explains that while there are multiple approaches for extending the half-life of GLP-1 agonists, “[l]iraglutide and semaglutide carry fatty acids, which facilitate binding to serum albumin thereby reducing their renal clearance.”²³²

²³⁰ EX1076 (Lorenz), 4014.

²³¹ EX1076 (Lorenz), 4014, Fig. 2a.

²³² EX1076 (Lorenz), 4014, Fig. 2.

155. Therefore, in view of Lorenz, a POSA would have looked to guidance and teachings related to the semaglutide compounds and structural modification strategies, including the use of fatty acid side chains to extend the half-life of GLP-1 and GIP agonist compounds (allowing for prolonged periods between doses).

156. In doing so, a POSA would have identified Lau as Novo Nordisk's original patent on the semaglutide compound, with guidance on structural strategies for extending half-life.

157. Similar to the illustration in Fig. 2a of Lorenz, Lau discloses specific peptide design choices to prolong half-life and extend dosing frequency, stating “there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g., once every second or third day[,] preferably once weekly, while retaining an acceptable clinical profile.”²³³ Lau also explains that the decreased dosing frequency is achieved by conjugating the lysine residue in position 20 (pro-peptide position 26) of GLP-1 to an albumin-binding moiety that increases the duration of action of the GLP-1 analogue, stating:

The invention provides a GLP-1 analog having a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37) (SEQ ID No 1), which is acylated with a moiety to the lysine residue in position 26, and where said

²³³ EX1009 (Lau), 1:31-34.

moiety comprises at least two acidic groups, wherein one acid group is attached terminally.²³⁴

158. Lau teaches that this approach to prolonging the action of the agonist is applicable not only to the preferred GLP-1 analogues depicted therein, but also to other peptides with additional modifications to the amino acid sequence but which remain insulintropic agents.²³⁵ Lau teaches this approach to prolonged duration of action is useful because the acylated GLP-1 analogues can bind to albumin and the GLP-1 receptor simultaneously, such that they retain adequate affinity for the receptor.²³⁶

159. As noted in the passage from Lau above, the specific design choices taught by Lau include (1) modifying at least one non-proteinogenic amino acid at positions 7 and/or 8 relative to the GLP-1 sequence; and (2) acylation of the lysine residue at GLP-1 position 26 (corresponding to position 20 of the GLP-1 agonist compound).

160. Regarding the design strategy related to modifying at least one non-proteinogenic amino acid at positions 7 and/or 8 relative to the GLP-1 sequence (positions 1-2 of the GLP-1 agonist compound), Lau provides preferred substitutions at the 7 and/or 8 position, preferably Aib (α -aminoisobutyric acid) at

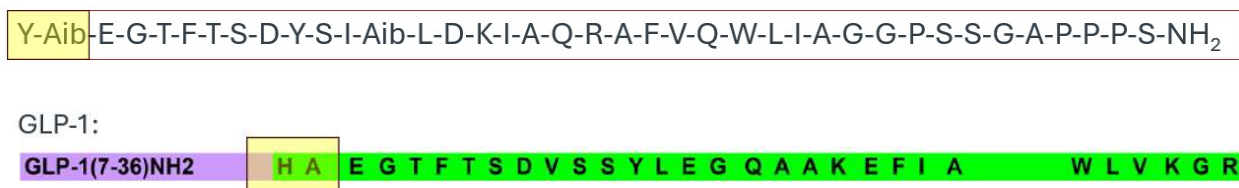
²³⁴ EX1009 (Lau), 2:1-5.

²³⁵ EX1009 (Lau), 3:8-4:8.

²³⁶ EX1009 (Lau), 6:6-22.

position 8 (corresponding to position 2 of the GLP-1 agonist compound).²³⁷ In fact, the semaglutide compound described in both Lorenz and Lau includes Aib at position 8 (position 2 of the GLP-1 agonist compound).²³⁸ Based on this disclosure, a POSA was motivated to utilize Aib as a non-proteogenic amino acid residue at position 8 (position 2 of the GLP-1 agonist compound), as Lau teaches that Aib is a preferred residue at that position and the semaglutide compound similarly incorporated Aib at position 2.

161. Below is an illustration of the peptide sequence rendered obvious by Alsina-Fernandez (lead compound/reference) and DiMarchi, which I have discussed previously:



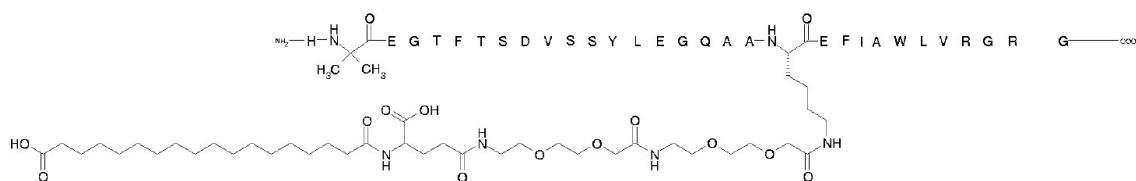
162. As I have highlighted in yellow, the peptide compound based on the teachings of Alsina-Fernandez in view of DiMarchi already incorporates modifications at positions 7 and 8 (positions 1 and 2 of the peptide compound), including the preferred Aib residue at position 2, meaning this design strategy was

²³⁷ EX1009 (Lau), 8:12-15; 9:1-10; 11:11-12; 17:13; 17:32; 18:29-30; 19:1-2; 19:25-26; 19:30-31.

²³⁸ See EX1076 (Lorenz), 4014, Fig. 2a; EX1009 (Lau), 47:4-22, Example 4.

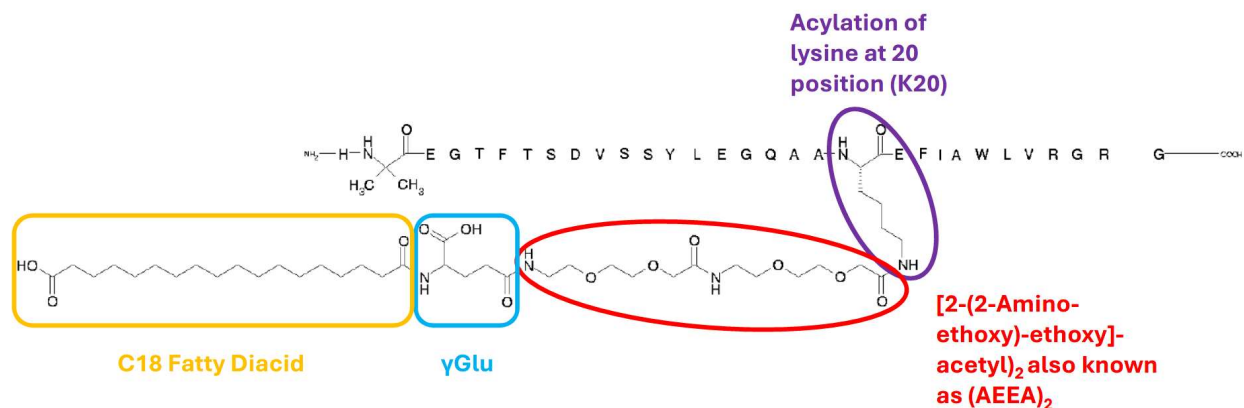
already incorporated into the compound formed by Alsina-Fernandez in view of DiMarchi.

163. Because this design strategy was already accounted for, a POSA would have then turned to the second design strategy described by Lau to prolong the duration of effect, namely acylation of the lysine residue at GLP-1 position 26 (corresponding to position 20 of the GLP-1 agonist compound). For reference, Example 4 of Lau illustrates the chemical structure for semaglutide, as shown below:²³⁹



164. To further illustrate, I have provided an annotated copy of the semaglutide structure, noting the acylation of the lysine at position 20 of the semaglutide molecule, as well as the specific components of the acylation moiety:

²³⁹ EX1009 (Lau), 47:4-22.

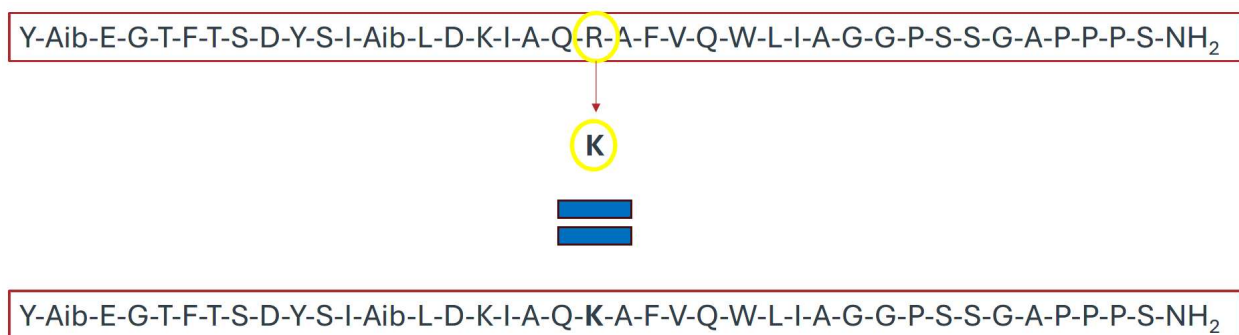


165. As I have noted above, the semaglutide structure is acylated at the lysine in position 20 (noted in purple), whereby the spacer is conjugated to the amine side chain of the lysine. Additionally, the spacer of semaglutide consists of both the 2-(2-amino-ethoxy)-ethoxy]-acetyl)₂ (noted in red) and the gamma-glutamate (noted in blue). Finally, semaglutide incorporates a C18 fatty diacid (noted in gold).

166. Turning first to semaglutide's incorporation of a lysine at the 20 position of the sequence, DiMarchi teaches that the Arg (R) present at position 20 in the Alsina-Fernandez/DiMarchi peptide can be replaced with a lysine (K), stating "[i]n some embodiments the amino acid at position 20 is substituted with Ser, Thr, **Lys**, Arg, Orn, Citrulline or AIB."²⁴⁰ Additionally, the native GLP-1 peptide has a lysine (Lys) residue at position 26 (i.e., position 20 of the GLP-1 agonist compound). As I have discussed previously, where possible, preserving

²⁴⁰ EX1017 (DiMarchi), 40:7-8. (Emphasis added).

native amino acid sequence is generally preferred, as it can help to minimize immunogenicity, so in this instance a POSA was further motivated to utilize Lys at position 26 (i.e., position 20 of the GLP-1 agonist compound) from among the options disclosed by DiMarchi. Further, because Lau expressly focuses its design strategy on acylation of a lysine (K) at position 26 relative to GLP-1 (i.e., position 20 of the GLP-1 agonist compound), a POSA was motivated to replace the arginine (R) in the Alsina-Fernandez/DiMarchi peptide with lysine (K), as that was permitted by the teachings of DiMarchi, and the semaglutide compound successfully incorporated this change, as shown in the illustration below:



167. Additionally, DiMarchi discusses that acylation can be achieved via a spacer (e.g., an amino acid, dipeptide, tripeptide, hydrophilic bifunctional spacer, hydrophobic bifunctional spacer), and that acylation can improve half-life and resistance to deactivation.²⁴¹ DiMarchi also states that “[a]cylation can be carried out at any position within the glucagon peptide, including any of positions 1-

²⁴¹ EX1017 (DiMarchi), 7:7-10, 56:3-8.

29.”²⁴² However, DiMarchi identifies preferred amino acids and locations for acylation, including the amino acid at position 20:

In a specific aspect of the invention, the glucagon peptide is modified to comprise an acyl group by direct acylation of an amine, hydroxyl, or thiol of a side chain of an amino acid of the glucagon peptide. In some embodiments, the glucagon peptide is directly acylated through the side chain amine, hydroxyl, or thiol of an amino acid. In some embodiments, acylation is at position 10, 20, 24, 29, or 40. In this regard, the acylated glucagon peptide can comprise the amino acid sequence of SEQ ID NO : 1 , or a modified amino acid sequence thereof comprising one or more of the amino acid modifications described herein, with at least one of the amino acids at positions 10, 20, 24, 29, and 40 modified to any amino acid comprising a side chain amine, hydroxyl, or thiol.²⁴³

DiMarchi’s disclosure of position 20 as a preferred amino acid to be acylated was consistent with not only the teachings in Lau related to semaglutide (directed to acylation specifically at the Lys²⁰ position), but also Madsen et al., which assessed the impact of acylating peptides with fatty acids of vary lengths on half-life, all of which were acylated at the lysine at position 26 of native GLP-1 (corresponding to position 20 of the GLP-1 agonist compound).²⁴⁴ Given all these factors, a POSA would have been motivated to acylate the lysine at position 20 of the Alsina-

²⁴² EX1017 (DiMarchi), 56:29-57:1; 58:8-17.

²⁴³ EX1017 (DiMarchi), at 58:8-17. (Emphasis added).

²⁴⁴ EX1079 (Madsen), 6126-6127.

Fernandez/DiMarchi peptide, and would reasonably expect that the lysine at position 20 could be successfully acylated.

168. DiMarchi also teaches that the spacer can be attached to the amine side chain of lysine (K), stating that “[i]n the instance in which the side chain amine of the spacer amino acid is acylated, the spacer amino acid is an amino acid comprising a side chain amine, e.g., an amino acid of Formula I (e.g., **Lys** or **Orn**).”²⁴⁵ Consequently, DiMarchi expressly contemplated the attachment of a spacer to the lysine at position 20, similar to the design strategy utilized for semaglutide (as described in Lau).

169. Regarding specific compounds to be utilized as the spacer, Lau explains that the spacer is a “hydrophilic linker” that separates the peptide and the albumin binding residue.²⁴⁶ In addition, many of the Examples of Lau (including, e.g., Examples 4, 5, 6, 10, 11, and 15) utilize a specific spacer compound, namely a [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu) spacer. To illustrate, I have provided the table below with the structure of each of the peptides of Examples 4, 5, 6, 10, 11, and 15, with the spacer moiety highlighted in yellow:²⁴⁷

<u>Example</u>	<u>Structure with Spacer Highlighted</u>
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²⁴⁵ EX1017 (DiMarchi), 60:19-23. (Emphasis added).

²⁴⁶ EX1009 (Lau), 6:22-24.

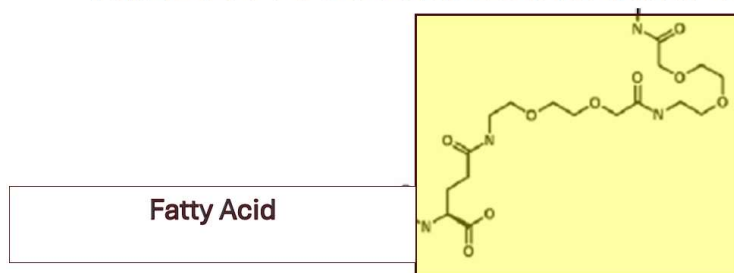
²⁴⁷ EX1009 (Lau), 47:4-9 (Example 4), 47:22-28 (Example 5), 48:12-18 (Example 6), 50:6-11 (Example 10), 50:22-28 (Example 11), 51:6-10 (Example 12), 52:12-16 (Example 15).

4	
5	
6	
10	
11	
12	
15	

170. As illustrated in the table above, Lau teaches the inclusion of the same [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu) spacer (also known as an AEEA-

AEEA- γ Glu spacer) to attach the fatty acid (of various lengths) to the lysine at the 20 position of the peptide (in the structures of Examples 4, 5, 6, 10, 11, 12, and 15, the lysine is represented by its full chemical structure to illustrate the binding position, rather than the shorthand “K”). Indeed, Example 4 above is the semaglutide compound, which is shown utilizing the same [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu) spacer, and using this spacer to attach a C18 fatty diacid to the peptide sequence. In view of the teachings of Lau and DiMarchi, and in view of Lau’s teachings that the semaglutide compound was shown to have an ~160-hour half-life (allowing for once weekly administration), a POSA would have been motivated to utilize the same [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu) spacer, attached to the lysine at the 20 position of the peptide based on the teachings of Alsina-Fernandez in view of DiMarchi and Lau. Additionally, a POSA would reasonably expect that this same spacer can be utilized in the Alsina-Fernandez/DiMarchi peptide, as it was shown to be successfully incorporated into semaglutide, and successfully extended the duration of action. I have illustrated this structural modification below (the [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu) spacer highlighted in yellow):

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-K-A-F-V-Q-W-L-I-A-G-G-P-S-S-G-A-P-P-S-NH₂



171. Moreover, DiMarchi teaches that the acyl group (used for the aforementioned acylation) may be a fatty acid, stating that “[i]n some embodiments, the acyl group is a fatty acid or bile acid, or salt there, e.g., a C4 to C30 fatty acid, a C8 to C24 fatty acid, cholic acid, a C4 to C30 alkyl, a C8 to C24 alkyl, or an alkyl comprising a steroid moiety of a bile acid.”²⁴⁸ In fact, DiMarchi specifically identifies C8 to C20 fatty acids as potential options, stating:

The acyl group of the acylated glucagon peptide can be of any size, e.g., any length carbon chain, and can be linear or branched. In some specific embodiments of the invention, the acyl group is a C4 to C30 fatty acid. For example, the acyl group can be any of a C4 fatty acid, C6 fatty acid, C8 fatty acid, C10 fatty acid, C12 fatty acid, C14 fatty acid, C16 fatty acid, C18 fatty acid, C20 fatty acid, C22 fatty acid, C24 fatty acid, C26 fatty acid, C28 fatty acid, or a C30 fatty acid. In some embodiments, the acyl group is **a C8 to C20 fatty acid**, e.g., a C14 fatty acid or a C16 fatty acid.²⁴⁹

172. DiMarchi’s teachings are entirely consistent with the teachings of Lau. Although Lau does not discuss specific fatty acids attached to the peptides via

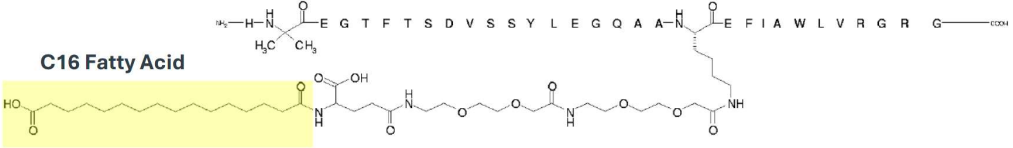
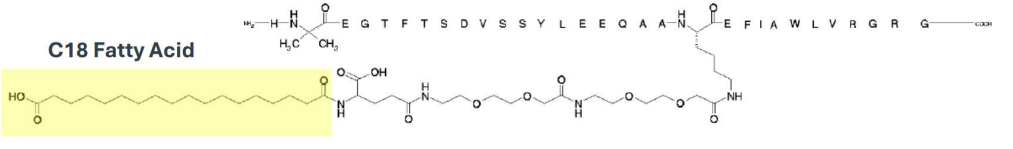
²⁴⁸ EX1017 (DiMarchi), 56:17-19.

²⁴⁹ EX1017 (DiMarchi), 64:7-13. (Emphasis added).

the spacer, the structures provided in the Examples of Lau illustrate that C16, C18 and C20 fatty acids (diacids) were preferably utilized. I have provided the table below to illustrate the fatty acids utilized in Lau's examples:²⁵⁰

<u>Example</u>	<u>Structure with Fatty Acid Highlighted</u>
4	C18 Fatty Acid
5	C20 Fatty Acid
6	C18 Fatty Acid
10	C18 Fatty Acid
11	C18 Fatty Acid

²⁵⁰ EX1009 (Lau), 47:4-9 (Example 4), 47:22-28 (Example 5), 48:12-18 (Example 6), 50:6-11 (Example 10), 50:22-28 (Example 11), 51:6-10 (Example 12), 52:12-16 (Example 15).

12	 C16 Fatty Acid
15	 C18 Fatty Acid

173. It is my understanding that one basis for obviousness is choosing something from a finite number of identified, predictable solutions, with a reasonable expectation of success. Here, DiMarchi and Lau both teach a small number of fatty acids that may be used as part of the albumin binding moiety, including primarily C8, C10, C12, C14, C16, C18, and C20 fatty acids, with special emphasis on C16, C18, and C20 fatty acids, as those were all utilized in the Examples of Lau, with the same AEEA-AEEA- γ Glu spacer. Further, it was established in the field that increasing the length of the fatty acid chain can enhance the half-life of glucagon-like peptide derivatives. As one example, Madsen et al. examined the impact of fatty acid chain length on the half-life and duration of GLP-1 compounds.²⁵¹ Specifically, Madsen assessed various peptide derivatives, all of which were derivatized at the lysine (K) at position 26 of the native GLP-1 sequence (corresponding to position 20 of the GLP-1 agonist

²⁵¹ See EX1079 (Madsen).

compound sequence, I have discussed previously) with a spacer and an acyl group.²⁵² This is the same conjugation strategy I discussed previously, with regard to Lau and Lorenz. Additionally, Madsen utilized a γ -Glu spacer in Compounds 1-6, which was attached to fatty acids of varying lengths, including C10, C11, C12, C14, C16, and C18 fatty acids (corresponding to Compounds 1, 2, 3, 4, 5, and 6, respectively).²⁵³ Madsen found that, as the length of the fatty acid attached to the spacer increases, the compound's half-life was prolonged, with half-life values of 0.8 hours for the C10 fatty acid; 5.1 hours for the C11 fatty acid; 7.6 hours for the C12 fatty acid; 9 hours for the C14 fatty acid; 16 hours for the C16 fatty acid; and 21 hours for the C18 fatty acid.²⁵⁴ Consequently, a POSA would view the results of Madsen as evidence that increasing the length of the fatty acid is generally expected to prolong the half-life of the GLP-1 compounds.

174. Based on the knowledge in the field, as exemplified by the disclosure of Madsen, in my opinion, a POSA would reasonably expect that the C16, C18, and C20 fatty acids described in Lau and DiMarchi could be utilized in the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau, and that the use of any of these fatty acids would be expected to provide a prolonged half-life,

²⁵² EX1079 (Madsen), 6126-6127.

²⁵³ EX1079 (Madsen), 6127.

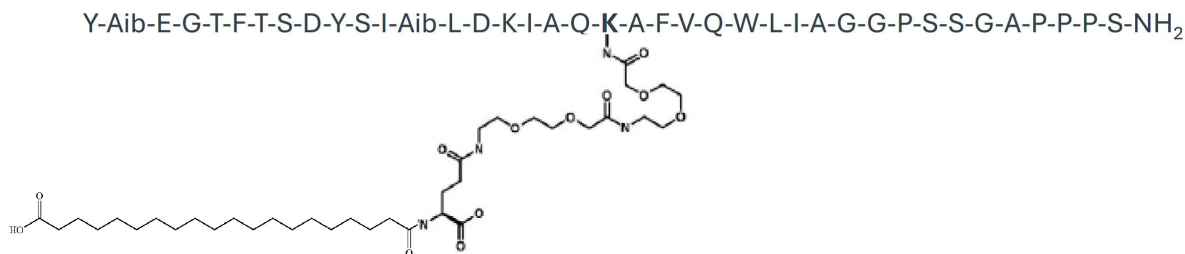
²⁵⁴ EX1079 (Madsen), 6127.

similar to what was achieved with the use of a C18 fatty acid in the semaglutide compound. In fact, DiMarchi expressly explains that acylation or alkylation of the glucagon peptide “[i]ncreas[es] solubility and/or duration of action nor half-life in circulation,”²⁵⁵ further supporting this expectation.

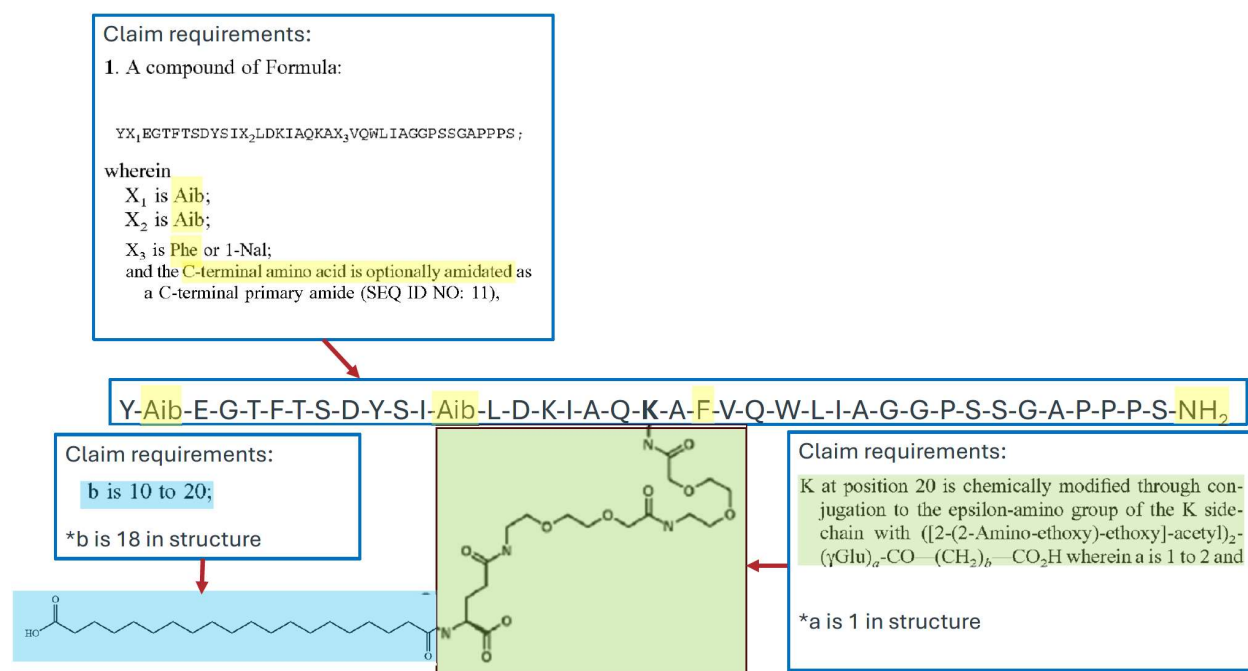
175. In view of these considerations, the acylation of the lysine (K) at position 20, with a spacer attached to a fatty acid (as was utilized in semaglutide) is precisely what was contemplated by DiMarchi and Lau, feeding both the motivation and reasonable expectation of success in utilizing this strategy to further modify the peptide of Alsina-Fernandez and DiMarchi. Based upon the guidance provided by Lau (in view of Lorenz), and the explicit disclosure in DiMarchi discussing an acyl group attached via a spacer, a POSA would have been motivated to include the same AEEA-AEEA-γGlu spacer from semaglutide, attaching it to the amine of the lysine (K) amino acid at position 20, and using the spacer to attach a fatty acid, especially the C16, C18, and C20 fatty acids utilized in the Examples of Lau.

176. To illustrate, I have provided the structure of the resulting peptide based on the teachings of Alsina-Fernandez in view of DiMarchi and Lau below. For purposes of this illustration, I have included a C20 fatty acid (though the use of a C16 and/or C18 fatty acid would also be obvious design choices based on Lau):

²⁵⁵ (DiMarchi), 8:12-14.



177. This peptide meets all the requirements of claim 1. Provided below I have annotated which portions of the structure correspond to the various requirements of claim 1:



178. Accordingly, it is my opinion that Alsina-Fernandez in view of DiMarchi and Lau render obvious a peptide, as shown above, that meets each and every structural limitation of claim 1. In addition, it is my opinion that a POSA would have been motivated to implement each of these substitutions/design strategies, and had a reasonable expectation of success in doing so, for all the

reasons I noted in my previous analysis. Therefore, it is my opinion that claim 1 is obvious over Alsina-Fernandez in view of DiMarchi and Lau.

B. Claim 2

179. It is my opinion that claim 2 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 2 is dependent from claim 1. My previous analysis for claim 1 is incorporated herein in its entirety.

180. The language of claim 2 is provided below:

2. The compound of claim 1, wherein X_3 is Phe.

181. Claim 2 requires that X_3 is Phe. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide having a Phe (“F”) residue at position 22 (the location of X_3). Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that X_3 is Phe, and it is my opinion that claim 2 is obvious over the prior art.

C. Claim 4

182. It is my opinion that claim 4 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 4 is dependent from claim 2. My previous analysis for claim 2 is incorporated herein in its entirety.

183. The language of claim 4 is provided below:

4. The compound of claim 2, wherein b is 14 to 18.

184. Claim 4 requires that b is 14 to 18. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide having a fatty acid attached to the AEEA-AEEA- γ Glu spacer. Additionally, as I illustrated in my claim 1 analysis, it was an obvious design choice for a POSA to utilize a C20 fatty acid based on the teachings of Lau. When the peptide includes a C20 fatty acid, the “b” value for the peptide is 18, corresponding to the 18 methylene units present in the C20 fatty acid.

185. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that “b is 14 to 18,” and it is my opinion that claim 4 is obvious over the prior art.

D. Claim 5

186. It is my opinion that claim 5 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 5 is dependent from claim 4. My previous analysis for claim 4 is incorporated herein in its entirety.

187. The language of claim 5 is provided below:

5. The compound of claim 4, wherein b is 16 to 18

188. Claim 5 requires that b is 16 to 18. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide having a fatty acid attached to the AEEA-AEEA- γ Glu spacer. Additionally, as I illustrated in my claim 1 analysis, it was an obvious design choice for a POSA to utilize a

C20 fatty acid based on the teachings of Lau. When the peptide includes a C20 fatty acid, the “b” value for the peptide is 18, corresponding to the 18 methylene units present in the C20 fatty acid.

189. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that “b is 16 to 18,” and it is my opinion that claim 5 is obvious over the prior art.

E. Claim 6

190. It is my opinion that claim 6 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 6 is dependent from claim 5. My previous analysis for claim 5 is incorporated herein in its entirety.

191. The language of claim 6 is provided below:

6. The compound of claim 5, wherein b is 18.

192. Claim 6 requires that b is 18. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide having a fatty acid attached to the AEEA-AEEA- γ Glu spacer. Additionally, as I illustrated in my claim 1 analysis, it was an obvious design choice for a POSA to utilize a C20 fatty acid based on the teachings of Lau. When the peptide includes a C20 fatty acid, the “b” value for the peptide is 18, corresponding to the 18 methylene units present in the C20 fatty acid.

193. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that “b is 18,” and it is my opinion that claim 6 is obvious over the prior art.

F. Claim 7

194. It is my opinion that claim 7 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 7 is dependent from claim 4. My previous analysis for claim 4 is incorporated herein in its entirety.

195. The language of claim 7 is provided below:

7. The compound of claim 4, wherein a is 1.

196. Claim 7 requires that a is 1. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide having a [2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu) spacer conjugated to the amine group side chain of the lysine (K) at position 20 of the sequence, meaning that there is a single γ-glutamyl group, and the “a” value for this compound is 1.

197. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that “a is 1,” and it is my opinion that claim 7 is obvious over the prior art.

G. Claim 9

198. It is my opinion that claim 9 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 9 is dependent from claim 4. My previous analysis for claim 4 is incorporated herein in its entirety.

199. The language of claim 9 is provided below:

9. The compound of claim 4, wherein the C-terminal amino acid is amidated as a C-terminal primary amide.

200. Claim 9 requires that the C-terminal amino acid is amidated as a C-terminal primary amide. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide whereby the C-terminal amino acid is amidated as a C-terminal primary amide (-NH₂).

201. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the requirement that “the C-terminal amino acid is amidated as a C-terminal primary amide,” and it is my opinion that claim 9 is obvious over the prior art.

H. Claim 10

202. It is my opinion that claim 10 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 10 is dependent from claim 1. My previous analysis for claim 1 is incorporated herein in its entirety.

203. Claim 10 recites the following:

10. The compound of claim 1, wherein

X₁ is Aib

X₂ is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO—(CH₂)₁₈—CO₂H;

X₃ is Phe;

and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3),

or a pharmaceutically acceptable salt thereof.

204. Claim 10 only varies from claim 1 in that the ([2-(2-amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁ is limited to a single compound (i.e., “a is 1”); the number of methylene groups in the -CO-(CH₂)₁₈-CO₂H fatty acid limited to 18 (i.e., “b is 18”); and the C-terminal amino acid is amidated as a C-terminal primary amide (as opposed to the C-terminal being optionally amidated in claim 1). For the same reasons I noted in my analysis of claim 7 (requiring that “a is 1”), claim 6 (requiring that “b is 18”), and claim 9 (requiring that “the C-terminal amino acid is amidated as a C-terminal primary amide”), Alsina-Fernandez in view of DiMarchi and Lau renders obvious a peptide whereby meeting all of these structural requirements.

205. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious a peptide compound meeting all the structural requirements of claim 10, and this claim is obvious over the prior art.

I. Claim 12

206. It is my opinion that claim 12 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. The language of claim 12 is provided below:

12. A pharmaceutical composition comprising the compound of claim 10 with a pharmaceutically acceptable carrier, diluent, or excipient.

207. Claim 12 is directed to a pharmaceutical composition the contains the compound of claim 10 in combination with a pharmaceutically acceptable carrier, diluent or excipient. As an initial matter, my previous analysis establishing the obviousness of the compound of claim 10 is incorporated herein in its entirety.

208. Alsina-Fernandez, DiMarchi, and Lau all teach and contemplate that the peptide compounds described in the respective references could be developed as pharmaceutical formulations. Specifically, Alsina-Fernandez states “this invention provides a pharmaceutical formulation comprising a peptide of the invention with a pharmaceutically acceptable carrier, diluent, or excipient.”²⁵⁶ Similarly, DiMarchi states “[s]terile pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent kits comprising devices are provided.”²⁵⁷ Lau teaches that “[i]t is possible that other ingredients may be present in the peptide pharmaceutical formulation of the present invention. Such additional

²⁵⁶ EX1007 (Alsina-Fernandez), 5:4-5.

²⁵⁷ EX1017 (DiMarchi), 17:22-23.

ingredients may include wetting agents, emulsifiers, antioxidants, bulking agents, tonicity modifiers, chelating agents, metal ions, oleaginous vehicles, proteins (e.g., human serum albumin, gelatine or proteins) and a zwitterion (e.g., an amino acid such as betaine, taurine, arginine, glycine, lysine, and histidine).”²⁵⁸

209. Consequently, all of Alsina-Fernandez, DiMarchi, and Lau teach that the peptides can be combined with a pharmaceutically acceptable carrier, diluent or excipient. A POSA would have been motivated to develop the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau as a pharmaceutical composition comprising the peptide and a pharmaceutically acceptable carrier, diluent or excipient, and would have had at least a reasonable expectation that the peptides could be successfully combined with a carrier, diluent, or excipient, as this is standard practice, and it was already shown that other peptides (e.g., exenatide, liraglutide, semaglutide, etc.) had been successfully developed as pharmaceutical compositions.

210. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “a pharmaceutical composition comprising the compound of claim 10 with a pharmaceutically acceptable carrier, diluent, or excipient,” and it is my opinion that claim 12 is obvious over the prior art.

²⁵⁸ EX1009 (Lau), 32:24-30.

J. Claim 13

211. It is my opinion that claim 13 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. The language of claim 13 is provided below:

13. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 10.

212. Claim 13 is directed to a method of treating type 2 diabetes mellitus (T2DM) by administering an effective amount of the compound of claim 10. As an initial matter, my previous analysis establishing the obviousness of the compound of claim 10 is incorporated herein in its entirety.

213. Alsina-Fernandez, DiMarchi, and Lau all teach and contemplate that the peptide compounds described in the respective references could be administered for the treatment of diabetes mellitus. Specifically, Alsina-Fernandez states that “[t]he present invention also provides a method for treating diabetes mellitus in a patient comprising administering to a patient in need of such treatment an effective amount of a peptide of the invention. The present invention further provides a method for treating non-insulin-dependent diabetes mellitus in a patient comprising administering to a patient in need of such treatment an effective amount of a peptide of the invention.”²⁵⁹ Non-insulin-dependent diabetes mellitus is also known as type 2 diabetes mellitus. Similarly, DiMarchi states that “[i]n

²⁵⁹ EX1007 (Alsina-Fernandez), 3:32-4:3.

some embodiments, a method of treating hyperglycemia, or a method of reducing weight gain or inducing weight loss is provided, which involves administering an effective amount of an aqueous solution comprising a glucagon peptide of the invention.... Such methods for treating hyperglycemia are expected to be useful for a variety of types of hyperglycemia, including diabetes, diabetes mellitus type I, diabetes mellitus type II, or gestational diabetes, either insulin-dependent or non-insulin-dependent, and reducing complications of diabetes including nephropathy, retinopathy and vascular disease.”²⁶⁰ Further, Lau states “[i]n another embodiment a compound according to the invention is used for the preparation of a medicament for delaying or preventing disease progression in type 2 diabetes.”²⁶¹

214. Consequently, Alsina-Fernandez, DiMarchi, and Lau all teach that the peptides can be administered in an effective amount for the treatment of type 2 diabetes mellitus. Based on these teachings, a POSA would have been motivated to administer the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau to patients with type 2 diabetes mellitus, and would have had a reasonable expectation of success in doing so.

215. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “[a] method of treating type 2 diabetes

²⁶⁰ EX1017 (DiMarchi), 97:8-19.

²⁶¹ EX1009 (Lau), 38:3-4.

mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 10,” and it is my opinion that claim 13 is obvious over the prior art.

K. Claim 14

216. It is my opinion that claim 14 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 14 is dependent from claim 13. My previous analysis for claim 13 is incorporated herein in its entirety.

217. The language of claim 14 is provided below:

14. The method of claim 13, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

218. Claim 14 requires that peptide compound of claim 10 is administered “simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.”

219. Alsina-Fernandez states that “[t]his invention also provides pharmaceutical compositions comprising a peptide of the invention with one or more pharmaceutically acceptable carriers, diluents, or excipients. In a particular embodiment, the composition further comprises one or more other therapeutic

agents.”²⁶² Alsina-Fernandez also states that “[c]urrent treatment for diabetes includes insulin secretagogues, such as sulfonylureas and glitinides....”²⁶³ Further, DiMarchi states that “[t]he glucagon peptides of the invention may be administered alone or in combination with other anti-diabetic or anti-obesity agents. Anti-diabetic agents known in the art or under investigation include insulin, sulfonylureas... biguanides such as metformin (Glucophage) or phenformin; thiazolidinediones such as rosiglitazone (Avandia), pioglitazone (Actos), or troglitazone (Rezulin)....”²⁶⁴

220. Consequently, Alsina-Fernandez and DiMarchi teach that the peptides can be administered in combination with other anti-diabetic agents, including sulfonylureas, metformin, and thiazolidinediones. Based on these teachings, a POSA would have been motivated to administer the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau to patients with type 2 diabetes mellitus, in combination with one or more of sulfonylureas, metformin, and thiazolidinediones, and would have had a reasonable expectation of success in doing so.

²⁶² EX1007 (Alsina-Fernandez), 5:18-21.

²⁶³ EX1007 (Alsina-Fernandez), 1:30-32.

²⁶⁴ EX1017 (DiMarchi), 100:23-30.

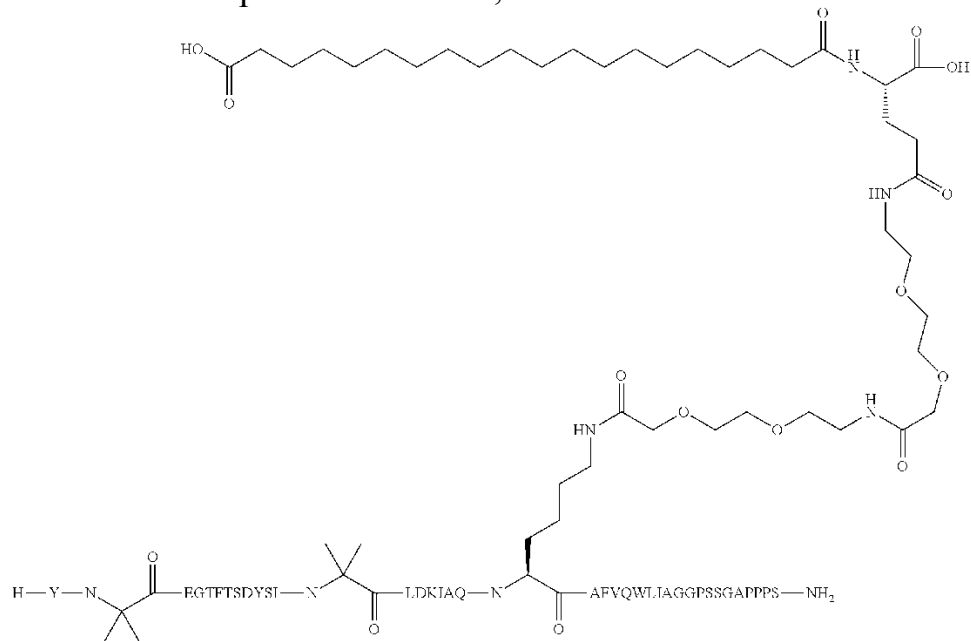
221. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters,” and it is my opinion that claim 14 is obvious over the prior art.

L. Claim 15

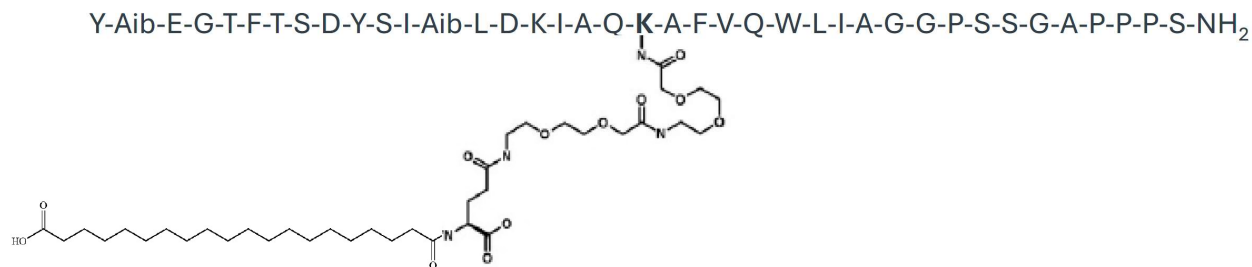
222. It is my opinion that claim 15 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 15 is dependent from claim 1. My previous analysis for claim 1 is incorporated herein in its entirety.

223. The language of claim 15 is provided below:

15. The compound of claim 1, wherein the Formula is



224. As I noted in my claim 1 analysis, Alsina-Fernandez in view of DiMarchi and Lau renders obvious the following peptide:



225. While the orientation and labeling of the peptide in my illustration of this compound is different than what is provided in claim 15, a POSA would nonetheless know that this peptide is the same compound with the same chemical structure as what is recited in claim 15.

226. Thus, for all the reasons I previously noted, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the specific peptide recited in claim 15, and it is my opinion that claim 15 is obvious over the prior art.

M. Claim 16

227. It is my opinion that claim 16 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. The language of claim 16 is provided below:

16. A pharmaceutical composition comprising the compound of claim 15 with a pharmaceutically acceptable carrier, diluent, or excipient.

228. Claim 16 is directed to a pharmaceutical composition containing the compound of claim 15 in combination with a pharmaceutically acceptable carrier,

diluent or excipient. As an initial matter, my previous analysis establishing the obviousness of the compound of claim 15 is incorporated herein in its entirety.

229. Alsina-Fernandez, DiMarchi, and Lau all teach and contemplate that the peptide compounds described in the respective references could be developed as pharmaceutical formulations. Specifically, Alsina-Fernandez states “this invention provides a pharmaceutical formulation comprising a peptide of the invention with a pharmaceutically acceptable carrier, diluent, or excipient.”²⁶⁵ Similarly, DiMarchi states “[s]terile pharmaceutical compositions comprising a pharmaceutically acceptable carrier or diluent kits comprising devices are provided.”²⁶⁶ Lau teaches that “[i]t is possible that other ingredients may be present in the peptide pharmaceutical formulation of the present invention. Such additional ingredients may include wetting agents, emulsifiers, antioxidants, bulking agents, tonicity modifiers, chelating agents, metal ions, oleaginous vehicles, proteins (e.g., human serum albumin, gelatine or proteins) and a zwitterion (e.g., an amino acid such as betaine, taurine, arginine, glycine, lysine, and histidine).”²⁶⁷

230. Consequently, all of Alsina-Fernandez, DiMarchi, and Lau teach that the peptides can be combined with a pharmaceutically acceptable carrier, diluent or

²⁶⁵ EX1007 (Alsina-Fernandez), 5:4-5.

²⁶⁶ EX1017 (DiMarchi), 17:22-23.

²⁶⁷ Lau at 32:24-29.

excipient. A POSA would have been motivated to develop the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau as a pharmaceutical composition comprising the peptide and a pharmaceutically acceptable carrier, diluent or excipient, and would have had at least a reasonable expectation that the peptides could be successfully combined with a carrier, diluent, or excipient, as this is standard practice, and it was already shown that other peptides (e.g., exenatide, liraglutide, semaglutide, etc.) had been successfully developed as pharmaceutical compositions.

231. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “a pharmaceutical composition comprising the compound of claim 15 with a pharmaceutically acceptable carrier, diluent, or excipient,” and it is my opinion that claim 16 is obvious over the prior art.

N. Claim 17

232. It is my opinion that claim 17 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. The language of claim 17 is provided below:

17. A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 15.

233. Claim 17 is directed to a method of treating type 2 diabetes mellitus (T2DM) by administering an effective amount of the compound of claim 15. As an

initial matter, my previous analysis establishing the obviousness of the compound of claim 15 is incorporated herein in its entirety.

234. Alsina-Fernandez, DiMarchi, and Lau all teach and contemplate that the peptide compounds described in the respective references could be administered for the treatment of diabetes mellitus. Specifically, Alsina-Fernandez states that “[t]he present invention also provides a method for treating diabetes mellitus in a patient comprising administering to a patient in need of such treatment an effective amount of a peptide of the invention. The present invention further provides a method for treating non-insulin-dependent diabetes mellitus in a patient comprising administering to a patient in need of such treatment an effective amount of a peptide of the invention.”²⁶⁸ Non-insulin-dependent diabetes mellitus is also known as type 2 diabetes mellitus. Similarly, DiMarchi states “[i]n some embodiments, a method of treating hyperglycemia, or a method of reducing weight gain or inducing weight loss is provided, which involves administering an effective amount of an aqueous solution comprising a glucagon peptide of the invention... Such methods for treating hyperglycemia are expected to be useful for a variety of types of hyperglycemia, including diabetes, diabetes mellitus type I, diabetes mellitus type II, or gestational diabetes, either insulin-dependent or non-insulin-dependent, and reducing complications of diabetes including nephropathy,

²⁶⁸ EX1007 (Alsina-Fernandez), 3:32 to 4:3.

retinopathy and vascular disease.”²⁶⁹ Further, Lau states “[i]n another embodiment a compound according to the invention is used for the preparation of a medicament for delaying or preventing disease progression in type 2 diabetes.”²⁷⁰

235. Consequently, Alsina-Fernandez, DiMarchi, and Lau all teach that the peptides can be administered in an effective amount for the treatment of type 2 diabetes mellitus. Based on these teachings, a POSA would have been motivated to administer the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau to patients with type 2 diabetes mellitus, and would have had a reasonable expectation of success in doing so.

236. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “a method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of the compound of claim 15,” and it is my opinion that claim 17 is obvious over the prior art.

O. Claim 18

237. It is my opinion that claim 18 is obvious over Alsina-Fernandez in view of DiMarchi and Lau. Claim 18 is dependent from claim 17. My previous analysis for claim 17 is incorporated herein in its entirety.

²⁶⁹ EX1017 (DiMarchi), 97:8-19.

²⁷⁰ EX1009 (Lau), 38:3-4.

238. The language of claim 18 is provided below:

18. The method of claim 17, further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.

239. Claim 18 requires that peptide compound of claim 15 is administered “simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters.”

240. Alsina-Fernandez states that “[t]his invention also provides pharmaceutical compositions comprising a peptide of the invention with one or more pharmaceutically acceptable carriers, diluents, or excipients. In a particular embodiment, the composition further comprises one or more other therapeutic agents.”²⁷¹ Alsina-Fernandez also states that “[c]urrent treatment for diabetes includes insulin secretagogues, such as sulfonylureas and glitinides....”²⁷² Further, DiMarchi states that “[t]he glucagon peptides of the invention may be administered alone or in combination with other anti-diabetic or anti-obesity agents. Anti-diabetic agents known in the art or under investigation include insulin,

²⁷¹ EX1007 (Alsina-Fernandez), 5:18-21.

²⁷² EX1007 (Alsina-Fernandez), 1:30-32.

sulfonylureas... biguanides such as metformin (Glucophage) or phenformin; thiazolidinediones such as rosiglitazone (Avandia), pioglitazone (Actos), or troglitazone (Rezulin)....”²⁷³

241. Consequently, Alsina-Fernandez and DiMarchi teach that the peptides can be administered in combination with other anti-diabetic agents, including sulfonylureas, metformin, and thiazolidinediones. Based on these teachings, a POSA would have been motivated to administer the peptide rendered obvious by Alsina-Fernandez in view of DiMarchi and Lau to patients with type 2 diabetes mellitus, in combination with one or more of sulfonylureas, metformin, and thiazolidinediones, and would have had a reasonable expectation of success in doing so.

242. Thus, Alsina-Fernandez in view of DiMarchi and Lau teaches and renders obvious the claimed requirement of “further comprising administering simultaneously, separately, or sequentially in combination with an effective amount of one or more agents selected from metformin, thiazolidinediones, sulfonylureas, dipeptidyl peptidase 4 inhibitors, and sodium glucose co-transporters,” and it is my opinion that claim 18 is obvious over the prior art.

X. SECONDARY CONSIDERATIONS

²⁷³ DiMarchi at 100:23-30.

243. I am informed that determining obviousness entails evaluating secondary considerations for indicia relevant to the determination of obviousness, if presented, but that there must be a nexus between evidence of these considerations and some aspect of the claim not already in the prior art. Where unexpected results are proffered as a secondary consideration of non-obviousness, I am informed that the results are relevant to an obviousness determination when they represent a difference in kind rather than degree as compared to the closest prior art.

244. I have reviewed the prosecution history of the '780 Patent but did not find any suggestion or assertion therein that the patentability of the claims is supported by any secondary considerations of non-obviousness.²⁷⁴

245. I also have reviewed the '780 Patent in its entirety, to assess for potential evidence of secondary considerations of non-obviousness. I did not find any secondary considerations indicative of non-obviousness in the '780 Patent.

246. The '780 Patent states in the specification that “there remains a need” to provide a balanced co-agonist of GIP and GLP-1 receptors, with selectivity over the glucagon receptor, and that a need allegedly remained for “a compound with balanced co-agonist activity of GIP and GLP-1 receptors which may provide

²⁷⁴ See Section IV.C. above.

weight loss given activity found in animal models.”²⁷⁵ However, these statements appear to be contradictory to the express disclosure of the '780 Patent, which explicitly cites to previous patent applications describing co-agonists of GIP/GLP-1, including, among others, WO 2011/119657 (i.e., Alsina-Fernandez). As I discussed previously, Alsina-Fernandez discloses the peptide compound of Example 2, which provided a strong (picomolar) binding affinity for both GIP binding (*see* K_i value reported in Table 1 of 0.023 nM)²⁷⁶ and GLP-1 binding (*see* K_i value reported in Table 2 of 0.059 nM),²⁷⁷ while at the same time providing a substantially higher K_i value for glucagon receptor binding (*see* Table 3, reporting a K_i value of >23,600 nM),²⁷⁸ representing substantially lower binding affinity for the glucagon receptor. In fact, a POSA would recognize that the similar binding affinities for GIP and GLP-1 (0.023 nM and 0.059 nM, respectively) represent a “balanced” co-agonism of GIP and GLP-1. Thus, Alsina-Fernandez expressly describes peptide compounds that functioned as a balanced co-agonist of GIP and GLP-1 receptors, while at the same time providing binding selectivity over the glucagon receptor. Additionally, Alsina-Fernandez also states that GIP and GLP-1 co-agonist peptides described therein can be used for inducing weight loss in

²⁷⁵ EX1001 ('780 Patent), 2:27-30.

²⁷⁶ EX1007 (Alsina-Fernandez), 13:6-10.

²⁷⁷ EX1007 (Alsina-Fernandez), 14:32-15:4.

²⁷⁸ EX1007 (Alsina-Fernandez), 16:22-25.

patients.²⁷⁹ Consequently, the alleged “need” within the art for a balanced co-agonist of GIP and GLP-1 with selectivity over glucagon receptors, and which can be used for weight loss, was previously described by the very reference cited in the background of the ’780 Patent (i.e., Alsina-Fernandez).

247. The ’780 Patent also states that a need remained to provide a compound with balanced co-agonist activity of GIP and GLP-1 receptors that delivers adequate stability against DPP IV and other forms of degradation, as well as allowing for potential once-weekly dosing in humans.²⁸⁰ However, as I have discussed previously in this declaration, the prior art disclosed strategies to achieve these very outcomes. DiMarchi teaches that adding a C-terminal extension peptide such as GGPSSGAPPPS at the 29 position not only enhanced the GLP-1 binding of the peptide, but it was well-known that the GGPSSGAPPPS motif had been successfully appended to DPP-IV-resistant GLP-1 compounds to improve their potency and metabolic stability without inducing undue immunogenicity.^{281,282} In fact, this same C-terminal motif GGPSSGAPPPS was also found in the FDA-approved GLP-1 receptor agonist exenatide, which was associated with reduced clearance, improvement in half-life, and less susceptibility to undesirable DPP-IV

²⁷⁹ EX1007 (Alsina-Fernandez), 4:10-12; 4:23-24.

²⁸⁰ EX1001 (’780 Patent), 2:34-41.

²⁸¹ EX1070 (Fineman), Abstract.

²⁸² EX1071 (Buse), 1700-1701, Abstract.

cleavage.²⁸³ Therefore, DiMarchi and others disclosed strategies to protect against DPP-IV degradation, while minimizing immunogenicity, and a POSA would not consider this to be an unmet need in the art.

248. Moreover, it was also known in the art from Lorenz and others, that semaglutide was a “next-generation GLP-1 analog” with an ~160-hour half-life (allowing for once weekly administration).²⁸⁴ As I discussed previously at length, Lau disclosed strategies to achieve this prolonged duration (i.e., conjugation, preferably at the lysine 20 position, with a lipophilic fatty acid (e.g., a C16, C18, or C20 fatty acid) to promote albumin binding and further extend the half-life). Consequently, Lorenz, Lau, and others disclosed strategies to prolong half-life to allow for once weekly administration of the peptide, and a POSA would not consider this to be an unmet need in the art.

249. While I agree that there was a motivation within the art to develop GIP/GLP-1 receptor co-agonists to provide a peptide that could be utilized as a treatment for diabetes and weight loss, while minimizing the side effects typically

²⁸³ See, e.g., EX1053 (“BYDUREON”), 9 (“...452 BYDUREON-treated patients (49%) had low titer antibodies (≤ 125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers.”); EX1054, 14 (“In the 30-week controlled trials 38% of patients had low titer anti-exenatide antibodies at 30 weeks. For this group, the level of glycemic control (HbA1c) was generally comparable to that observed in those without antibody titers.”).

²⁸⁴ EX1076 (Lorenz), 4014.

associated with GLP-1 receptor agonists (i.e., nausea), and also allowing for a prolonged duration that would require fewer injections of the peptide (e.g., once-weekly administration/injection), the structural modifications and strategies needed to achieve these ends were well-known, and do not represent a long felt, but unmet need within art.

250. I also assessed the data disclosed in the '780 Patent to determine whether the applicants provided any evidence of surprising and unexpected results that would overcome the *prima facie* obviousness of the claims. It is my opinion that the '780 Patent has provided no evidence of surprising and unexpected results that would overcome the obviousness of the challenged claims.

251. As I discussed previously in section IV.B, which I am incorporating herein, the '780 Patent provides a number of examples directed to the synthesis of specific peptide compounds, with varying amino acid sequences (*see* Examples 1-7).²⁸⁵ The '780 Patent includes only a single example (Example 8) providing an assessment of the *in vitro* and *in vivo* properties of the peptide compounds described in the patent. Specifically, Example 8 provides a number of assessments, whereby the exemplary peptides of Examples 1-8 were assessed for their binding properties to human GIP receptor, GLP-1 receptor, and glucagon receptor, as well as effective concentrations (EC₅₀), as compared to native GIP, GLP-1, and

²⁸⁵ EX1001 ('780 Patent), 8:56-13:67.

glucagon controls.²⁸⁶ While the '780 Patent makes general reference to “control” compounds for certain assessments of the exemplary peptides,²⁸⁷ in only one instance does the '780 Patent provide testing and a comparison to a known prior art peptide.

252. Specifically, the '780 Patent provides several comparisons to the prior art semaglutide compound; however, by the '780 Patent's own admission, semaglutide is a known selective GLP-1 receptor agonist (i.e., is not a co-agonist of GIP and GLP-1).²⁸⁸ Thus, none of the assessments provided in the '780 Patent compare the example peptides to the closest prior art, namely other GIP/GLP-1 receptor co-agonists. The '780 Patent admits that the prior art previously disclosed co-agonists of GIP and GLP-1 (“[c]ertain GIP analogs have been described as exhibiting both GIP and GLP-1 activity in WO 2013/164483, WO 2014/192284, and WO 2011/119657”).²⁸⁹ The co-agonists described in these previous applications are “closer” prior art than the semaglutide compound, as these compounds were acknowledged to have co-agonist properties. The '780 Patent

²⁸⁶ EX1001 ('780 Patent), 16:60-17:34, Table 2.

²⁸⁷ See EX1001 ('780 Patent), 19:48-49 (referencing a “C18-acylated human GLP-2 control,” but not specifying the structure of the compound); and 20:63-64 (referencing a “GIP/GLP-1 co-agonist Example from WO 2011/119657,” but not explaining which of the example compounds of WO 2011/119657 was assessed, or whether the example from WO 2011/119657 was pegylated, which is known to have an adverse impact on immunogenicity).

²⁸⁸ EX1001 ('780 Patent), 8:23-26.

²⁸⁹ EX1001 ('780 Patent), 1:55-57.

inventors were clearly aware of these prior art co-agonist peptides, yet elected to only include examples comparing the example peptides to controls and semaglutide (again, a peptide that is not considered a co-agonist).

253. The '780 Patent asserts that the Example 1 peptide affected murine metabolic rate compared to control, and that semaglutide “had no effect on metabolic rate.”²⁹⁰ But again, the peptide of Example 1 of the '780 Patent is a GIP/GLP-1 co-agonist, while semaglutide is not. As described in the background of the '780 Patent, both GIP and GLP-1 impact metabolic health (e.g., glucose homeostasis, insulin secretion, gastric emptying, etc.).²⁹¹ Consequently, a peptide that is an agonist for both GIP and GLP-1 would be expected to provide an increased metabolic response as compared to a compound that is a selective GLP-1 receptor agonist.

254. Throughout the examples, the '780 Patent provides a number of comparisons and tests between the peptides of Examples 1-8 and semaglutide (as well as comparison to non-peptide controls), as reported in Tables 7-14.²⁹² In no instance did the '780 Patent compare the peptides of Examples 1-8 to other known co-agonists of GIP and GLP-1.

²⁹⁰ EX1001 ('780 Patent), 25:55-26:61.

²⁹¹ EX1001 ('780 Patent), 1:3-36.

²⁹² EX1001 ('780 Patent), 22:40-27:40.

255. Additionally, the data reported in the examples are all based on very small experimental groups, likely contributing to the inconsistency in results, and lack of reproducibility. For example, in Example 8, Tables 8-9, the 30 nmol/kg dose of semaglutide provided wide-ranging results, in one instance (Table 8) reporting a % change from starting body weight of -14.20 ± 1.01 , and a % change from starting fat mass of -21.90 ± 2.07 , whereas in another instance (Table 9) the '780 Patent reports that the same 30 nmol/kg dose of semaglutide provided a % change from starting body weight of -17.03 ± 0.98 , and a % change from starting fat mass of -35.94 ± 4.09 .²⁹³ A POSA will understand that achieving different results when repeating the same experiment suggests that the results are likely the product of a small test group size, and must view any such results as requiring further testing (likely with larger test group sizes) before any firm conclusions can be made based on the data.

256. Similarly, the 30 nmol/kg dose of semaglutide provided wide-ranging results when assessing the impact on blood glucose, plasma cholesterol, and plasma triglycerides, as reported in Tables 11 and 12.²⁹⁴ Again, this would lead a

²⁹³ EX1001('780 Patent), Table 8 (-14.20 ± 1.01 % change in starting weight and -21.90 ± 2.07 % change in fat mass), Table 9 (-17.03 ± 0.98 % change in starting weight and -35.94 ± 4.09 % change in fat mass).

²⁹⁴ EX1001 ('780 Patent), Table 11 (blood glucose 146.8 ± 8.43 mg/dl, plasma cholesterol 229.8 ± 10.96 mg/dl, plasma triglycerides 27.9 ± 6.01 mg/dl), Table 12 (blood glucose 136.3 ± 3.81 mg/dl, plasma cholesterol 161.0 ± 13.92 mg/dl, plasma triglycerides 67.63 ± 23.40 mg/dl).

POSA to view the results provided in the Examples with skepticism, and would prevent any reliable conclusions from being drawn from the data.

257. Even beyond the reproducibility issues of the data in Tables 7-14, the results of the various assessments generally suggest that the peptides of the Examples performed similarly to semaglutide. For example, the '780 Patent reports that improved glucose tolerance achieved by the Example 1 peptide was “essentially the same” as that of semaglutide, and projected that a 1 mg dose of semaglutide would be equivalent to a 1.3 mg dose of the Example 1 peptide in humans.²⁹⁵ Additionally, when the '780 Patent reported *in vivo* insulin secretion in a rat model following intravenous glucose for Example peptides 1-3 and 5-8, again compared to semaglutide, there were not any meaningful differences in activity among the GIP/GLP-1 receptor co-agonists tested.²⁹⁶

258. In the one example where the '780 Patent attempted to assess immunogenicity, the patent failed to specify what prior art peptide the claimed peptides were being compared to (the patent only states that the peptide was compared to an example from WO 2011/119657).²⁹⁷ As an initial matter, the '780 Patent does not provide any of the underlying data that were used for this

²⁹⁵ EX1001 ('780 Patent), 21:58-22:17.

²⁹⁶ EX1001 ('780 Patent), 22:18-55 & Table 7.

²⁹⁷ EX1001 ('780 Patent), 20:45-21:7.

assessment (which leaves a POSA with skepticism as to the conclusions drawn from the assessment). Rather, the '780 Patent states that the peptide of Example 1 provided an EpiMatrix score (a predictive tool designed to measure potential immune response to a compound) of +1.13, which was lower than the score of +29.5 for “[a] GIP/GLP-1 co-agonist Example from WO 2011/119567,” suggesting a lower risk for immunogenicity with the peptide of Example 1. However, WO 2011/119567 discusses a number of embodiments that were PEGylated, and PEGylated drug compounds were known to have a high immunogenic potential.²⁹⁸ Thus, a POSA would need to know the exact example peptide from WO 2011/119567 that was used for this comparison, as well as the underlying data, before any meaningful conclusions can be made.

259. Moreover, the '780 Patent discloses that the *in vivo* pharmacokinetic properties of various peptide compounds within the scope of the claims were assessed in cynomolgus monkeys.²⁹⁹ The '780 Patent reports that the peptide of Example 1 provided a mean half-life of 55 hours, which was alleged to “support[] the potential of once-weekly dosing for Example 1.”³⁰⁰ However, there are multiple

²⁹⁸ EX1022 (Garay), Abstract, 1320 (reporting that reported that up to 25% of healthy blood donors (*i.e.* no indication of ever being previously treated with a PEGylated drug), and up to 89% of patients treated with PEGylated drug have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds).

²⁹⁹ EX1001 ('780 Patent), 21:10-13.

³⁰⁰ EX1001 ('780 Patent), 21:34-37.

issues with the reporting of this data. First, outside of a mention of the results in the specification, the '780 Patent provides little of the underlying data that was provided for Example 1 – Table 6 of the '780 Patent, which reports the test data for the peptides of Examples 2, 3, 6, 7, and 8, provides no data for the peptide of Example 1.³⁰¹ Additionally, Table 6 reports that the data used to assess the mean half-life was based on a treatment group size of only *two* cynomolgus monkeys (i.e., $n = 2$).³⁰² With such a small treatment group size, a POSA cannot make any meaningful conclusions. Further, once again the '780 Patent failed to provide any data whereby the *in vivo* pharmacokinetic properties of Examples 1, 2, 3, 6, 7, or 8 was compared to the closest prior art, such as the GIP/GLP-1 co-agonists of WO 2013/164483, WO 2014/192284, and/or WO 2011/119657. In addition, while the '780 Patent asserts that the mean half-life of 55 hours supports potential once-weekly administration, it is nonetheless considerably less than the half-life achieved with semaglutide (~160 hours), and, while semaglutide is not the closest prior art, a POSA would still not look at these values as rising to the level of a surprising or unexpected result. Consequently, in my opinion the '780 Patent's reporting of *in vivo* pharmacokinetics in a very small group (i.e., $n = 2$) of

³⁰¹ EX1001 ('780 Patent), 21:34-55.

³⁰² EX1001 ('780 Patent), 21:34-55.

cynomolgus monkeys does not provide any evidence of surprising or unexpected results.

260. In total, the data provided by the '780 Patent indicates precisely what a POSA would have expected, namely that the claimed peptide compounds can be utilized as co-agonists of GIP and GLP-1, and generally provided binding affinities and other metabolic properties similar to those achieved with semaglutide.

However, none of the data in the '780 Patent demonstrates any unexpected result, much less any difference in kind, as compared to the closest prior art (i.e., other co-agonists of GIP and GLP-1).

261. Additionally, to the extent that the co-agonists of GIP/GLP-1 described in the '780 patent provide any alleged “synergism,” this synergism was expected based on the teachings of DiMarchi (“[i]n vivo data disclosed herein demonstrate that the combination of GIP agonist activity with GLP-1 agonist activity produces a greater effect on weight reduction than GLP-1 alone”)³⁰³ and Finan (“co-agonism at both of the receptors for the incretin hormones glucagon-like peptide-1 (GLP-1) and glucose-dependent insulintropic polypeptide (GIP)...[t]his unimolecular dual incretin...demonstrated enhanced antihyperglycemic and insulintropic efficacy relative to selective GLP-1

³⁰³ EX1017 (DiMarchi), 2:19-21.

agonists[,] [and] this superior efficacy translated across rodent models of obesity and diabetes”).³⁰⁴

262. In conclusion, I am not aware of any secondary considerations that would change my opinion that claims 1-2, 4-7, 9-10, and 12-18 of the '780 Patent are *prima facie* obvious over Alsina-Fernandez in view of DiMarchi and Lau.

XI. CO-PENDING IPR2025-01024

263. I am aware of IPR2025-01024 filed by Empower Clinic Services, L.L.C. (d/b/a Empower Pharmacy) against the '780 Patent on May 22, 2025 (hereinafter “the Empower IPR petition”). I have reviewed the Empower IPR petition, as well as the supporting declaration of Dr. Virginia Cornish, Ph.D. (hereinafter “the Cornish declaration”). While my declaration is provided in support of the IPR petition filed by BPI, and focuses on a prior art combination distinct from that provided in the Empower IPR Petition and the Cornish declaration, I nonetheless agree with her analysis, and have adopted parts of her discussion herein.

XII. CONCLUDING STATEMENTS

264. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be

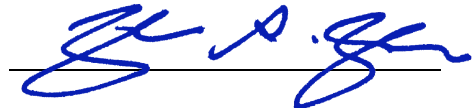
³⁰⁴ EX1061 (Finan), abstract.

subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for cross-examination within the United States during the time allotted for cross-examination.

265. 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 are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: 4 August 2025

By:



Zhaohui Sunny Zhou, Ph.D.

XIII. APPENDIX

Exhibit No	Description
1001	U.S. Patent No. 9,474,780.
1002	Declaration of Virginia Cornish, PH.D. in support of IPR2025-01024.
1003	<i>Intentionally left blank.</i>
1004	Prosecution History (Excerpts) of U.S. Patent No. 9,474,780.
1005	WO 2016/111971 Search Report.
1006	WO 2016/111971 Written Opinion.
1007	WO 2011/119657 A1 Publication (Alsina-Fernandez).
1008	WO 2013/164483 A1 Publication (Just).
1009	WO 2006/097537 A2 Publication (Lau).
1010	WO 2014/202727 A1 Publication.
1011	Fields G. B. Introduction to peptide synthesis. <i>Current protocols in protein science, Chapter 18</i> , 2002; 18.1.1–18.1.9.
1012	US 2015/0299281 A1 Publication.
1013	SAXENDA (liraglutide) injection drug label (Dec. 2014) (“SAXENDA”) available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf .
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