

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

EMPOWER CLINIC SERVICES, L.L.C.
(d/b/a Empower Pharmacy),
Petitioner,

v.

ELI LILLY & CO.,
Patent Owner.

IPR2025-01024
Patent No. 9,474,780

DECLARATION OF VIRGINIA CORNISH, PH.D.

**BPI Labs, LLC, EX1002
BPI Labs, LLC v. Eli Lilly and Company
IPR2025-01346**

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I, Virginia W. Cornish, declare as follows:

I. QUALIFICATIONS

1. I am the Helena Rubinstein Chair in the Department of Chemistry and a founding member of the Department of Systems Biology at Columbia University. I have held faculty appointments from 1999 to the present. My research for over two decades has been directed toward understanding and developing combined synthetic chemistry and DNA technologies to expand the synthetic capabilities of living cells. This research included the development of protein tags for live cellular imaging, non-canonical amino acid translation, and the engineering and development of living yeast biosensors with modular G-protein coupled receptor (GPCR)s and therapeutic yeast that secrete therapeutic peptides and proteins for diagnostic and human health applications.

2. I graduated summa cum laude from Columbia University with a B.A. in Biochemistry in 1991, and subsequently earned my Ph.D. in Chemistry with Professor Peter Schultz at the University of California at Berkeley in 1996. As an undergraduate I did my coursework under some of the leaders in the field of Organic Chemistry and synthesized a photoaffinity reagent that was part of a large collaboration in Professor Ron Breslow's laboratory to develop a first in class histone deacetylase inhibitor that ultimately was acquired by Merck Pharmaceuticals. My Ph.D. research spanned organic chemistry, protein

chemistry, and molecular biology. I helped develop the Genetic Code Expansion technology in the Schultz laboratory by applying the technology to address fundamental questions in protein stability and enzyme mechanism. In my final publication with Professor Schultz, I demonstrated that this technology could be utilized to introduce a chemical group called a ketone, rather than a natural proteinogenic amino acid side chain, site specifically into a protein. The ketone could then be tagged with a fluorescent hydrazine label or other chemical/reactive moiety, providing a modular strategy for labeling proteins with different chemical groups. This work was foundational to what would later become the field of bio-orthogonal chemistry.

3. I was subsequently a Postdoctoral Fellow in the Biology Department at the Massachusetts Institute of Technology from 1996-1999 under Professor Bob Sauer. Professor Sauer allowed me to initiate my independent research and it was there that I started my pioneering work in synthetic biology in the yeast *Saccharomyces cerevisiae*, investigating how genetic selections can be adapted for the *in vivo* directed evolution of chemistries unnatural to the cell. This discovery was coined “chemical complementation” and was the foundation of later research developments including the TMP-tag. The Department of Chemistry at Columbia University invited me to apply for a faculty position a few months after I started my post-doc. They offered me the position at the end of my interview and allowed

me to complete two years of post-doctoral work at M.I.T.

4. Currently, I serve as a Professor within the Department of Chemistry and Systems Biology, as well as a principal investigator of a research laboratory at Columbia University. Relevant highlights of my scientific contributions include the discovery of a novel translation mechanism of an unnatural oligomer reassigning multiple sense codons in a row using a purified translation system modified tRNAs. This discovery was the basis of several manuscripts and research projects working towards the goal of synthesis of oligomers other than the natural polypeptides by translational machinery. At the time, this had been a long-standing challenge in the field and opened up an entire sub-field in the unnatural amino acid community. I have over 100 research publications and my work has been published in numerous prestigious journals, including *Proceedings of the National Academy of Sciences USA*, *Nature Methods*, *Science Advances*, *Nature Communications*, *Journal of the American Chemical Society*, *Science*, *Nature*, and *Cell*.

5. I have received many research grants to fund my work and have been the principal investigator for multiple major research and training grants from the NIH, NSF, DARPA, USDA, and private foundations. Research grants for which I have been the principal investigator include: “General and High-Throughput Small Molecule Screens and Selections for Metabolic Engineering”

NIH R01 GM134293-01A1; and “Living Yeast Sense-Respond Therapeutic Communities Engineered with Synthetic Biology” NIH MIRA GMAABT2642.

6. I have also been the recipient of many prestigious awards within the field, including an NSF Career Award (2000), a Sloan Foundation Fellowship (2003), the Columbia College John Jay Award (2005), the Protein Society Irving Sigal Young Investigator Award (2009), the American Chemical Society Pfizer Award in Enzyme Chemistry (2009), and an HHMI Gilliam Adviser (2021).

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

II. SCOPE OF WORK

8. I am informed that Empower Clinic Services, L.L.C. (d/b/a Empower Pharmacy) (“Empower”) is filing a petition with the United States Patent and Trademark Office for *Inter Partes* Review of U.S. Patent No. 9,474,780 to ’780 patent (“Bokvist et al.,” EX1001, the “challenged patent”). Wilson Sonsini retained me on behalf of Empower as a technical expert in this matter to provide expert opinions regarding the ’780 patent.

9. My opinions are based on my specialized education, training, knowledge, skills, training, and experience in peptide chemistry as well as on the

¹ EX1003, *Curriculum Vitae* of Dr. Virginia W. Cornish, Ph.D.

materials cited in this declaration. For convenience, documents cited in this declaration are listed in Appendix II at the end of my declaration. I reserve the opportunity to address any additional facts, documents, or arguments subsequently presented.

10. Empower is compensating me at the rate of \$750 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

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

12. I have been advised that a claimed invention is not patentable for obviousness 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 claimed invention was made to the person of ordinary skill in the art (“POSA”) to which the subject matter of the invention pertains.

13. I understand that a determination of obviousness requires inquiries into: (i) the scope and content of the art when the claimed invention was made; (ii) the differences between the art and the claims at issue; (iii) the level of ordinary skill in the pertinent art when the claimed invention was made; and, to the extent any exist, (iv) secondary considerations indicating non-obviousness.

14. I understand that hindsight must not be used when comparing the prior art to the claimed invention for obviousness. Thus, a conclusion of obviousness must be firmly based on the knowledge and skill of the artisan at the time the claimed invention was made, without the use of post-filing knowledge.

15. I understand that a prima facie case of obviousness may be established when the claimed compounds have very close structural similarity and a similar utility to one or more prior art compounds and the prior art discloses a suitably operative process for making the compounds. Obviousness in this circumstance is established based on the motivation of one skilled in the art to make compounds similar in structure that are expected to have similar properties. 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 facially obvious.

16. However, the facial obviousness of structurally similar compounds may be overcome where: (1) there is no specific or significant utility known for the prior art compounds; (2) there is no reasonable expectation the new compound would have any properties similar to the prior art compounds motivating synthesis of the new compound; (3) the prior art teaches away from the new compound; or (4) reliable evidence demonstrates that the claimed compounds possess unexpectedly advantageous or superior properties different in kind from the properties of the prior art compounds. If the prior art compound does, in fact,

possess a particular benefit, even though the benefit is not recognized in the prior art, the patentee's recognition of the benefit is not itself sufficient to distinguish the claimed compound from the prior art.

17. I understand that compounds which are position isomers 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.

18. I understand that a finding of obviousness based on modifying an existing compound may be premised on selecting a particular compound as a lead compound, which is a compound that is a most promising compound for further development, and then optimizing one or more properties of that compound. I

understand that evaluation of a compound as a lead compound involves accounting for both the positive and negative properties of the compound, but that the law does not require identification of a single lead compound. In other words, a lead compound need not be the single best compound, so long as it was a most promising compound for further development from which the prior art did not teach away.

19. I understand that an obviousness case premised on combining different references requires some rational underpinning for combining the cited references with a reasonable expectation of successfully obtaining thereby what is claimed. I further understand that obviousness also may be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the claimed invention. Obviousness may be shown by demonstrating that the person of ordinary skill in the art would have combined the teachings of more than one element disclosed by prior art.

20. I understand that the following examples are approaches and rationales that may be considered in determining whether a piece of prior art would have been combined with other prior art or with other information within a skilled artisan's knowledge:

- (i) combining prior-art elements according to known methods to yield predictable results;
- (ii) substituting one known element for another to obtain predictable

results;

- (iii) using a known technique to improve similar devices (methods, or products) in the same way;
- (iv) applying a known technique to a known device (method, or product) that was ready for improvement to yield predictable results;
- (v) applying a technique or approach that would have been “obvious to try” (*i.e.*, choosing something from a finite number of identified, predictable solutions, with a reasonable expectation of success);
- (vi) applying variations based on known work in one field of endeavor for use in either the same field or a different one, based on design incentives or other market forces, if the variations would have been predictable to one of ordinary skill in the art; or
- (vii) acting upon some teaching, suggestion, or motivation in the prior art to modify the prior-art reference or to combine prior-art reference teachings thereby arriving at the claimed invention.

21. I have been instructed that “secondary considerations” will be considered when present. Counsel have informed me that such secondary considerations, where evident, may include: (i) commercial success of a product due to the merits of the claimed invention; (ii) a long-felt but unsatisfied need for the claimed invention; (iii) failure of others to find the solution provided by the claimed invention; (iv) deliberate copying of the claimed invention by others; (v) unexpected results achieved by the claimed invention; (vi) praise of the claimed invention by others skilled in the art; (vii) lack of independent, simultaneous invention within a comparatively short span of time; and (viii) teaching away from

the claimed invention in the prior art. I am informed that secondary considerations are relevant where there is a nexus between the evidence and the claimed invention.

22. I am informed that the patent owner, Eli Lilly & Co. (“Lilly”), bears the burden to produce evidence of secondary considerations indicating non-obviousness.

IV. OVERVIEW OF ’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 and glucose-dependent insulintropic polypeptide (GIP) and Glucagon-like peptide-1 (GLP-1), and may be useful for treating type 2 diabetes mellitus (T2D).”³ The challenged patent admits that both GIP and GLP-1 are natural incretins (i.e., they stimulate insulin secretion) that are critical for glucose homeostasis.⁴ In normal physiology, the patent explains, GIP and GLP-1 are secreted from the gut following a meal, and enhance insulin secretion, nutrient disposal, and sensation of satiety.⁵ The patent

² EX1001, [54].

³ EX1001, [57], 1:1-8.

⁴ EX1001, 1:28-31.

⁵ EX1001, 1:20-36.

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. First, the patent asserts that currently marketed incretin mimetics and dipeptidyl peptidase IV (DPP-IV) inhibitors used to treat T2D “only utilize a single established mechanism of action for glycemic control,” but that a “compound for T2D is needed that utilizes a dual mechanism of action.”⁸ The patent elaborates that “GIP alone has a very modest glucose-lowering ability in type 2 diabetic humans.”⁹ Second, the patent asserts that dosing of GLP-1 analogues has been found to be limited by adverse effects, such as nausea, vomiting, and elevated corticosterone levels, often preventing dosing from reaching full efficacy for glycemic control and weight loss.¹⁰ Third, native GIP and GLP-1 are inactivated rapidly by the ubiquitous DPP-IV protease, making them useful only for short-term

⁶ EX1001, 1:21-28.

⁷ EX1001, 1:25-28.

⁸ EX1001, 1:15-20.

⁹ EX1001, 1:40-41.

¹⁰ EX1001, 1:36-40, 2:13-22.

metabolic control.¹¹

25. Though the patent admits that certain GIP analogues exhibit dual GIP/GLP-1 activity, it asserts that there remained a need to provide a compound that is a balanced co-agonist of GIP and GLP-1 receptors, supports once-weekly dosing in humans, is selective against glucagon and GLP-2 receptors, provides weight loss, and delivers adequate stability against DPP-IV and other forms of degradation while still maintaining a low immunogenicity potential.¹² 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 2:3.¹³

26. The '780 patent presents “an embodiment of the present invention” in the form of “a compound of Formula I,” the amino acids in the peptide being represented by the sequence shown below.¹⁴

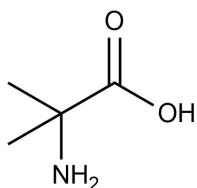
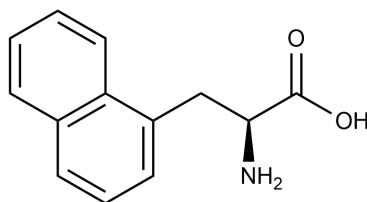
1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	I	A	Q	K	A	X ₃	V	Q	W	L	I	A	G	G	P	S	S	G	A	P	P	P	S

¹¹ EX1001, 1:41-44.

¹² EX1001, 2:28-41, 1:45-54.

¹³ EX1001, 6:36-43.

¹⁴ EX1001, 2:53-65, claim 1 (X₃ is Phe or 1-Naphthylalanine (1-Nal); K²⁰ is conjugated at the ε-amino group 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). Aib is 2-Aminoisobutyric acid.

2-Aminoisobutyric acid (Aib)¹⁵S-1-Naphthylalanine (1-Nal)¹⁶

In Formula I, the C-terminal amino acid is optionally amidated as a C-terminal primary amide.¹⁷

27. The patent also acknowledges sequences of native human GIP and human GLP-1, which I have reproduced below, followed by the sequence for SEQ ID No: 3 (a sequence satisfying all claims except claims 3, 11). For purposes of comparison of the patent's Formula I sequence to prior art GIP and GLP-1, I have used green font to identify amino acid residues that are identical (or homologous, e.g., Aib for A) in both endogenous ligands. These all are adopted in Formula I. I also used light and dark blue, respectively, to identify residues appearing naturally in GIP or GLP-1 that are adopted in Formula I.

Human GIP

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q

Human GLP-1

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30
H	A	E	G	T	F	I	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R

¹⁵ Aib is 2-Aminoisobutyric acid. *See also, e.g.* EX1009, 47:5-28.

¹⁶ 1-Nal is 1-Naphthylalanine.

¹⁷ *Id.*

SEQ ID NO: 3

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Y	A	E	G	T	F	I	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

28. The claimed sequence is very similar to endogenous human GIP, with substitutions at positions 14, 18, and 20 borrowed from endogenous human GLP-1 and additional substitutions at positions 21, 24, and 27. Residues 29-39 of the claimed sequence are identical to the natural C-terminal motif found in exenatide, the first FDA-approved GLP-1 receptor agonist derived from Gila monster saliva. I have used a purple font to identify this C-terminal motif.¹⁸ These natural ligands, and the known structure-activity-relationship for GIP and GLP-1 receptor agonism, is discussed in detail below.

29. 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

¹⁸ Thum A., Hupe-Sodmann K., Göke R., Voigt K., Göke B., McGregor G.P. Endoproteolysis by isolated membrane peptidases reveal metabolic stability of glucagon-like peptide-1 analogs, exendins-3 and -4. *Exp Clin Endocrinol Diabetes*. **2002** May;110(3):113-8, (hereinafter “Thum,” EX1069). Thum was published in 2002 in the peer-reviewed periodical *Exp Clin Endocrinol Diabetes*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1069, 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.”).

skill in the art.”¹⁹ The '780 patent further acknowledges that pharmaceutical compositions for administering the resulting peptides “are well known in the art.”²⁰ I agree that preparing and formulating the peptides using methods well known in the art was well within the skill of in the art.

A. Claims of '780 patent

30. The '780 patent lists 18 claims.²¹ I understand that the claims define the invention for purposes of performing a patentability analysis. Claims 2-18 all depend directly or indirectly from claim 1. I am informed that a claim that depends from one or more other claims incorporates all of the limitations of the claim(s) on which it depends. As such, each of the claims (1-18) requires “a compound of Formula” corresponding to Formula I, discussed above.

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	I	A	Q	K	A	X ₃	V	Q	W	L	I	A	G	G	P	S	S	G	A	P	P	P	S

X₃ = Phe or 1-Nal

K²⁰-conjugated ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_α-CO-(CH₂)_b-CO₂H

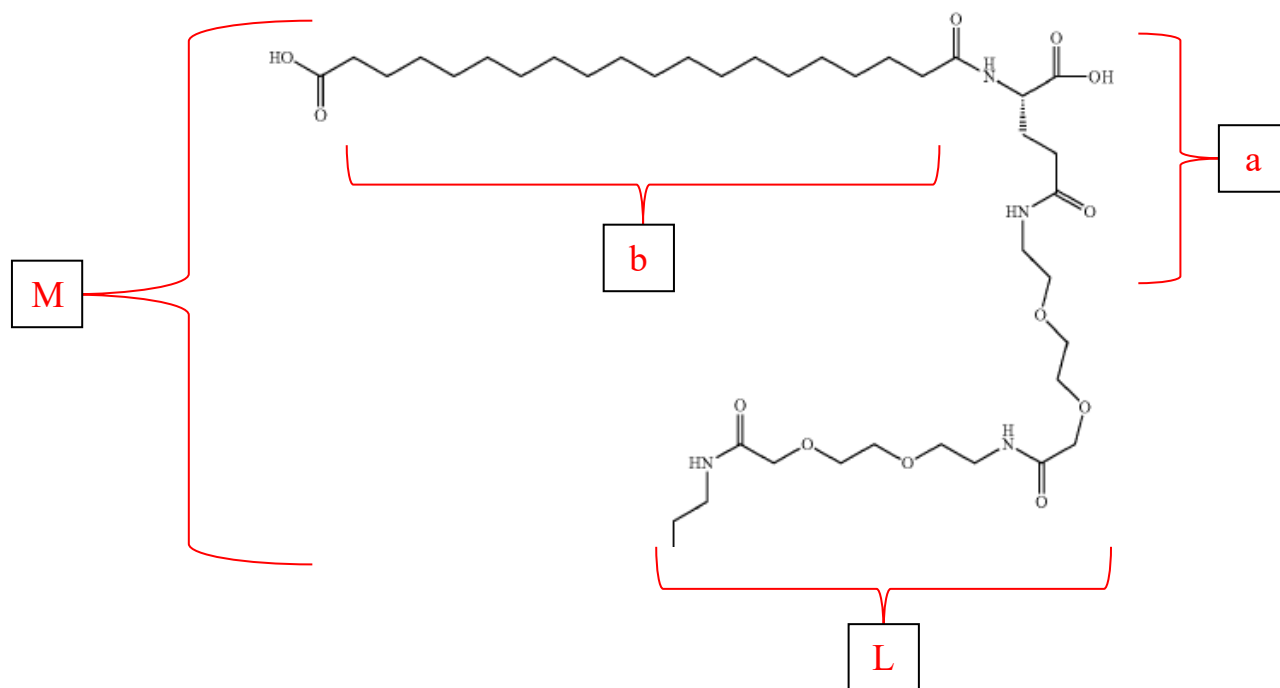
α = 1 to 2

b = 10 to 20.

¹⁹ EX1001, 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).

²⁰ EX1001, 7:45-64 (citing *Remington's Pharmaceutical Sciences*, 21st ed., Lippincott, Williams & Wilkins, 2006) and others).

²¹ EX1001, Claims.



M = albumin binding moiety²²

L = linker

a = γ Glu

b = methylene units in fatty acid chain

31. Claims 2-3 respectively limit the X₃ residue to Phe or 1-Nal. Claims 4-6 specify the number of repeating methylene units in the fatty acid chain. Claims 7-8 recite the number of (γ Glu) units in the linker. Claim 9 recites the compound as a C-terminal primary amide. Claim 10 recites and claim 15 depicts a combination of claims 6, 7, and 9 (SEQ ID NO: 3). Claim 11 recites a combination of claims 6,

²² EX1001, 7:19-23 (“The linker comprises [2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ Glu)_a wherein a is 1 to 2. The fatty acid and the gamma-glutamic acid in the linker act as albumin binders, and provide the potential to generate long-acting compounds.”).

8, and 9 (SEQ ID NO: 4). Claims 12 and 16 recite generic excipient categories. 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 17 recite combination administration with other active ingredients (e.g., metformin).

32. I discuss these limitations in more detail below.

B. Data in the '780 Patent

33. The '780 patent reports creating 8 example peptides within the scope of claim 1 and provides results for certain *in vitro* and *in vivo* experiments for some of these peptides. In some cases, the '780 patent provides certain activity results in some of those assays for one or more semaglutide treatments. In none of the activity assays does the '780 patent provide a comparator to a prior art GIP/GLP-1 receptor dual agonist, much less to the closest prior art.

34. For example, the patent asserts that the Example 1 peptide affected murine metabolic rate compared to control where semaglutide did not.²³ This experiment merely highlights that Example 1 is a GIP/GLP-1 receptor dual agonist and that semaglutide is not. This was not unexpected. The patent's plasma corticosterone measurements similarly fail to provide any comparison to a prior art

²³ EX1001, 25:55-26:61.

GIP/GLP-1 receptor dual agonist, much less a comparison to the closest prior art.²⁴

35. Most of the experiments (e.g., Tables 7-14) are designed to illustrate that the claimed peptides for which data is provided reduced body weight, fat mass, blood glucose, plasma cholesterol, triglycerides, or gastric emptying as compared to control. Even where statistical error measurements are provided, the patent's data reflects relatively large amounts of apparent experimental error when the same experiment is repeated, suggesting a lack of reproducibility in the data. For example, Tables 8-9 illustrate that the same dose of semaglutide (e.g., 30 nmol/kg) produced widely varying results when the assay was repeated.²⁵ Despite the reported error measurements, repetition of the same experiment that obtains numerically different results suggests the numerical differences are artifacts of experimental error. Tables 11-12 similarly provide numerically different results for semaglutide using the same 30 nmol/kg dose.²⁶ It would be a mistake to accept the patent's results as necessarily demonstrating actual differences between peptides.

²⁴ EX1001, 27:40-28:17 & Table 15.

²⁵ EX1001, 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).

²⁶ EX1001, 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).

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 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 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 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.

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.

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

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.

36. Importantly, different data in certain models (e.g., Tables 1-5 and 15) was not reliably reflected in clinical outcomes (e.g., Tables 7-14). This was not unexpected. Overall, the tested peptides within the scope of the claims appear to provide similar results to one another where data is provided, and the claimed peptides generally achieved similar biological outcomes regardless of any perceived differences in binding affinity or agonist “balance,” in vitro potency, or half-life, etc.

37. Among other things, the patent reports data from a study intended to

demonstrate *in vitro* binding potency (K_i) of the eight example peptides for Human GLP-1 and GIP receptors using “cloned human glucagon-like peptide 1 receptor (hGLP-1R)...isolated from 293HEK membranes.”²⁷ It also reports data from a study intended to evaluate *in vitro* functional activity towards human GIP, GLP-1, and glucagon receptors using HEK-293 clonal cell lines.²⁸ Next, it reports data from a study intended to evaluate functional activation of cells expressing hGIP-R to the exclusion of GLP-1 to generate cellular cAMP in incretin-secreting cell lines.²⁹ Next, it reports data from a study intended to evaluate intracellular cAMP generated in HEK293 cells transiently expressing hGLP-2R.³⁰ Next, it reports data from a study intended to evaluate insulin secretion in GIP and GLP-1-expressing rodent islet cells.³¹ The patent reports that improved glucose tolerance achieved by the Example 1 peptide was nearly identical to that of semaglutide and predicted that a 1.3 mg dose of Example 1 peptide would be equivalent to a 1 mg dose of semaglutide in humans for this purpose.³² The patent similarly reported *in vivo* insulin secretion in a rat model following intravenous glucose for Example

²⁷ EX1001, 14:28-16:59 & Table 1.

²⁸ EX1001, 16:60-17:67 & Table 2.

²⁹ EX1001, 18:1-19:14 & Table 3.

³⁰ EX1001, 19:15-67 & Table 4.

³¹ EX1001, 20:1-44 & Table 5.

³² EX1001, 21:58-22:17.

peptides 1-3 and 5-8 and semaglutide.³³ Overall, the claimed peptides for which data was provided appear to be active in the models applied but do not persuasively establish any persistent activity differences among the GIP/GLP-1 receptor dual agonists tested.

TABLE 1

Receptor Binding Affinity, K _i , nM (SEM, n)				
Compound	Human GIP-R	Human GLP-1R	Absolute ratio of hGLP-1R/hGIP-R	Molar ratio of hGLP-1R/hGIP-R
Example 1	34.4 (5.0, n = 8)	232 (40, n = 8)	6.7	1.48
GIP, 1-42	0.175 (0.022, n = 8)	>175 (n = 14)	>1000	
GLP-1, 7-36-NH ₂	>100 (n = 15)	0.793 (0.099, n = 8)	<0.008	
Example 3	26.7 (2.3, n = 17)	427 (33, n = 17)	16	3.53
Example 6	44.2 (3.6, n = 14)	365 (28, n = 14)	8.3	1.83
Example 7	46.1 (5.9, n = 11)	352 (39, n = 11)	7.6	1.68
Example 8	67.5 (9.9, n = 6)	307 (35, n = 6)	4.5	0.99
Example 4	40.7 (5.1, n = 7)	714 (76, n = 7)	17.5	3.86
Example 2	63.9 (11.8, n = 8)	344 (60, n = 8)	5.4	1.19
Example 5	17.8 (3.0, n = 5)	158 (32, n = 5)	8.9	1.96

Means are expressed as geometric means with the standard error of the mean (SEM) and the number of replicates (n) indicated in parenthesis. A qualifier (>) indicates data did not reach 50% inhibition and the K_i is calculated using the highest concentration tested in the assay.

TABLE 2

Functional Potency (EC ₅₀) against human GIP, GLP-1, and glucagon receptors.						
Compound	Human GIP-R		Human GLP-1R		Human GCGR	
	EC ₅₀ , nM ± SEM (n)	E _{max} , %	EC ₅₀ , nM ± SEM (n)	E _{max} , %	EC ₅₀ , nM ± SEM, (n)	E _{max} , %
Example 1	11.0 ± 0.9 (17)	97.9 ± 3.0	71.2 ± 7.2 (17)	85.2 ± 4.4	>1000 (13)	ND
Example 3	3.15 ± 0.34 (14)	106 ± 3	33.9 ± 3.2 (14)	96.2 ± 6.2	>1000 (10)	ND
Example 6	4.40 ± 0.71 (13)	106 ± 3	28.4 ± 4.2 (13)	104 ± 4	>1000 (9)	ND
Example 7	8.07 ± 0.70 (17)	106 ± 3	35.5 ± 2.6 (17)	97.2 ± 3.4	>1000 (13)	ND
Example 8	21.1 ± 2.7 (14)	108 ± 4	57.9 ± 6.8 (13)	88.4 ± 2.3	>1000 (10)	ND
Example 4	3.76 ± 0.83 (6)	102 ± 3	66.9 ± 14.9 (6)	100 ± 5	>1000 (2)	ND
Example 2	17.5 ± 2.0 (13)	94.7 ± 2.0	75.7 ± 6.0 (13)	98.2 ± 5.5	>1000 (9)	ND
Example 5	8.76 ± 0.86 (10)	105 ± 2	70.9 ± 9.7 (10)	105 ± 4	>1000 (10)	ND
hGLP-1(7-36)NH ₂			0.176 ± 0.015 (17)	102 ± 2		
hGIP(1-42)NH ₂	0.135 ± 0.010 (17)	100 ± 1				
hGlucagon					0.0208 ± 0.0024 (13)	115 ± 2

Means for EC₅₀ are expressed as geometric means +/- standard error of the mean (SEM) with the number of replicates (n) indicated in parenthesis.

Means for E_{max} are expressed as the arithmetic mean +/- standard error.

ND signifies that agonist activity was not detected.

A qualifier (>) indicates that an EC₅₀ could not be determined.

All values shown are to three significant digits

TABLE 3

EC50 in GLUTag cells.	
Compound	Average EC50, nM (n)
Example 3	1610 (1)
Example 7	2746 (1)
Example 4	2186 (1)
Example 2	2918 (1)
Example 1	1494 (2)
Native GIP	11.62 (3)

TABLE 4

GLP-2R functional activity measurement in HEK293 cells.		
Compound	Rel EC50 (nM)	n
GLP2-C ₁₈ -diacid	1.857	4
Example 3	199.3	4
Example 7	1,800	4
Example 4	405	2
Example 1	238	4
Example 2	1612	2

³³ EX1001, 22:18-55 & Table 7.

TABLE 5

Rodent Islet Insulin Secretion		
Compound	Mean ED50 (nM)	N
Rat islet insulin secretion		
Example 3	34.9	2
Example 1	15.5	3
Mouse islet insulin secretion		
Example 3	58.9	2
Example 6	51.4	1
Example 7	11.3	1
Example 4	3.5	1
Example 2	30.0	1
Example 1	47.2	2

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%

TABLE 6

Mean Pharmacokinetic Parameters Following a Single Subcutaneous Dose of 0.2 mg/kg to Male Cynomolgus Monkeys					
Compound	Mean T _{1/2} (hr)	Mean T _{max} (hr)	Mean C _{max} (µg/mL)	Mean AUC _{0-∞} (hr*µg/mL)	Mean CL/F (mL/hr/kg)
Example 3	34	8	3.0	153	1.3
Example 7	31	6	2.9	136	1.5
Example 6	23	4	2.2	72.3	2.8
Example 8	23	10	1.0	42.8	4.7
Example 2	43	24	2.1	173	1.2

n = 2,
AUC_{0-∞} = area under the curve from 0 to infinity,
CL/F = clearance/bioavailability,
T_{max} = time to maximum concentration,
C_{max} = maximum plasma concentration,
T_{1/2} = half-life.

TABLE 15

Plasma corticosterone analysis in Sprague Dawley Rats		
Compound	Corticosterone (ng/ml)	
	Mean	SEM
Vehicle	60.78	8.41
10 nmol/kg Semaglutide	274.57	42.06
3 nmol/kg Example 1	52.21	19.39
10 nmol/kg Example 1	32.46	9.78
30 nmol/kg Example 1	31.35	5.86

38. Aside from activity assays in certain models, the patent predicted or evaluated certain properties. For example, the patent predicts that the claimed peptides are not overly immunogenic and may be less immunogenic than another peptide.³⁴ As I explain below, these immunogenicity predictions would be expected by the skilled artisan.

39. In another example, the patent used very small sample sizes to begin to evaluate pharmacokinetics of some of the claimed peptides in cynomolgus

³⁴ EX1001, 20:45-21:7.

monkeys.³⁵ Due to the small sample sizes, a POSA would be hesitant to conclude the half-lives of these compounds are materially different from one another. As an aggregate, however, they support what would have been predicted by a POSA before the critical date: that the claimed compounds would be effectively administered using a dosing frequency less than once-per-day, including once-weekly, comparably to what was accomplished in the prior art.

40. Accordingly, none of the data in the challenged patent demonstrates any unexpected result, much less any difference in kind, as compared to the closest prior art.

C. Prosecution History of '780 patent

41. I am informed that communications between the patent application and the patent office (called the prosecution history) that led to the '780 patent (EX1004, excerpts) may be relevant understanding the claims. I understand that the application that led to the '780 patent ("the '791 application") was filed on January 5, 2016.³⁶ 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. 62/101,488.³⁷ For the purposes of my opinions,

³⁵ EX1001, 21:8-57 & Table 6. (n = 2).

³⁶ EX1001, 22.

³⁷ *Id.*, 60.

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.

42. Just 6 months after the '791 application was filed, the Examiner allowed the claims.³⁸ The prosecution history indicates that the Applicant received Patent Prosecution Highway designation and was therefore treated as “special.”³⁹ The “special” notification identified an April 25, 2016 prior art search conducted by the European Patent Office (EPO) in PCT/US2016/012124. The April 25, 2016, EPO search report considered only three references, only considered them as defining the general state of the art, and contained no analysis of any particular disclosures in any of them.⁴⁰

43. The U.S. Examiner’s consideration was only marginally longer. The U.S. Examiner considered a total of just thirteen publications, all of which were supplied by the Applicant (nothing identified by the Examiner).⁴¹ The Applicant did not submit for consideration EX1007 or EX1009, which are discussed in further detail below. Accordingly, the Examiner does not appear to have had the benefit of the disclosures of these references.

³⁸ EX1004, 22 (July 28, 2016).

³⁹ EX1004, 48-50.

⁴⁰ EX1005, (WO 2016/111,971), 46-48; EX1006, (Written opinion), 4.

⁴¹ EX1004, 36-39.

44. In allowing the claims, the Examiner discussed only one reference, 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 “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.⁴² 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.⁴³ The Examiner’s brief exploration of this single reference did not identify important prior art teachings establishing effective structure-activity relationships (“SARs”) for dual GIP/GLP-1 agonism effective for treating diabetes and obesity.

45. For example, the Examiner did not identify prior art teaching Gln as an appropriate residue at position 24 for preparation of an effective dual GIP/GLP-1 agonist or demonstrate awareness that employment of Gln at position 24 was strongly supported by the known, prior art SAR for GIP/GLP-1 dual agonism. Moreover, the Examiner demonstrated a lack of awareness of prior art teaching the Gln amino acid as a favorable substitution at position 24 expected to preserve the amino acid properties indicated at that position for dual GIP/GLP-1 agonism as

⁴² EX1004, 27-29.

⁴³ *Id.*

effective for treating diabetes and obesity.⁴⁴

46. The Examiner also did not identify prior art disclosure that Ile was a common and accepted prior art amino acid residue at position 17 for making a very potent and effective dual GIP/GLP-1 agonist effective for treating diabetes and obesity, and that this residue was particularly appropriate when the Lys residue for linking to an albumin-binding moiety was situated at position 20 rather than at position 17, as expressly taught in the prior art.⁴⁵

47. The Examiner did not identify prior art disclosure that the C-terminal motif (GGPSSGAPPPS) of the well-known prior art molecule exenatide worked well in *in vitro* and *in vivo* assays for dual GIP/GLP-1 agonism and was strongly indicated to a POSA by known, prior art SAR for dual GIP/GLP-1 agonism effective for treating diabetes and obesity.⁴⁶

48. The Examiner did not identify prior art teaching the specific albumin-binding moiety recited in the instant application, though this specific albumin-binding moiety was in fact disclosed in the prior art for the same purpose for which the challenged patent employed it. Nor did the Examiner identify prior art teaching

⁴⁴ EX1008, [0049]-[0050] (Gln is a conservative substitution for N at position 24). *See also* discussion of EX1008 in Sections VIII.B and IX.A.1 below.

⁴⁵ EX1008, [0065]-[0066]. *See also* discussion of EX1008 in Section VIII.B below.

⁴⁶ *See* discussion of EX1008 in Sections VIII.B and IX.A.1 below, and discussion of exenatide C-terminal motif in Section VII.C below.

the very parameters for the albumin-binding moiety employed in the challenged patent.

49. The Examiner did not identify prior art disclosure that Ile and Gly worked well at positions 27 and 29, respectively, for dual GIP/GLP-1 agonism, and was strongly indicated to a POSA by known, prior art SAR for dual GIP/GLP-1 agonism effective for treating diabetes and obesity.

50. In summary, though the Examiner stated that the one prior art reference discussed by the Examiner “encompasses” the claimed peptide⁴⁷ (with the exception of the Gln at position 24 and the particular albumin-binding moiety), the Examiner did not understand that the prior art discloses exactly these elements for exactly these purposes, and that known, prior art SAR strongly indicated the entire peptide sequence for dual GIP/GLP-1 agonism effective for treating diabetes and obesity. I discuss below in detail such salient prior art teachings that the Examiner’s evaluation failed to consider during prosecution, including disclosures in EX1007 and EX1009, and which demonstrate factual error in the Examiner’s conclusions.

51. The full text of the Examiner’s statements is reproduced below:⁴⁸

The closest prior art of Just et al. (US 2015/0299281 A1; WO

⁴⁷ EX1004, 28.

⁴⁸ Any bold text in a quote in this declaration has been added for emphasis unless indicated otherwise.

2013/164483) teaches GIP-GLP1 dual acting receptor agonists, which are closely related to the instantly claimed compounds. The genus of GIP-GLP1 co-agonists taught in the prior art (Formula I, para. [0044]) **differs from the compounds claimed in this application at position 24**. The prior art defines position 24 as Asn, Glu, Arg, or Lys, whereas the instant claims require position 24 to be Gln. Just et al. do not teach or suggest substituting Gln for the amino acids at position 24.

Just et al. teach that the GIP-GLP1 co-agonists can be conjugated with a lipophilic substituent to one or more of amino acid positions 16, 17, 19, 20, 24, 27, 28, 30 and 32 (para. [0111]), but do not teach the specific lipophilic substituent recited in the instant application.

In order to arrive at the instantly claimed compounds, one of ordinary skill in the art would have to **substitute Gln at position 24 and a moiety** of ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ -Glu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H as the lipophilic substituent. There is no teaching or suggestion in Just et al. to do so. Even if there were, it would require hindsight reasoning to make the compounds claimed in this application because all of the preferred embodiments and species disclosed in Just et al. differ from the instant compounds at additional positions. In other words, although **with the exception of amino acid at position 24 and the lipophilic substituent, the broad genus of Just et al. encompasses the claimed compounds**, the preferred embodiments, sub-genera, and species have several more differences.

For example, position 17 in Just et al. is preferably lysine, not isoleucine. In addition, position 27 in Just et al. is preferably Leu, Glu, or Val, not isoleucine. In addition, position 29 in Just et al. is preferably Gln or Ala, not Gly. See Formulae II(b), II(c), and II(d) and the species of Table 2 of Just et al. In addition, most of the species discloses [sic] in Just et al. lack the GPSSGAPPPS sequence at positions 30-39 (see Tables 1 and 2). In addition, the species in Just et al. that are conjugated to a lipophilic substituent, are conjugated to hexadecanoyl-isoGlu [sic] at lysine 17, not at lysine 20 (see Table 2).

Therefore, in order to make the instantly claimed compounds one of ordinary skill in the art would have to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different from those preferred and reduced to practice in Just et al. Then, one of ordinary skill in the art would have to substitute a Gln at

position 24 and a moiety of ([2-(2-Amino-ethoxy)-ethoxy]acetyl)₂-(γ -Glu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H for the lipophilic substituent, but not make any other changes. To do so would require hindsight reasoning. Thus the claimed compounds are both novel and unobvious over Just et al. With respect to the method claim, since the products are both novel and unobvious, methods of using these products are also both novel and unobvious.

V. LEVEL OF ORDINARY SKILL

52. 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.⁴⁹ Unless otherwise specifically noted, all of my opinions expressed here regarding the skilled artisan apply to the skilled artisan as of January 9, 2015.

53. By virtue of my education, experience, and training, I am familiar with the level of ordinary skill in the art of '780 patent. A POSA as of January 9, 2015, would typically have a Ph.D. in chemistry or 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

⁴⁹ See Section IV.C, above.

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 '780 patent itself.⁵⁰

54. Furthermore, a POSA would have been familiar with prior art pertaining to cell signaling peptides, their biochemistry, and cell-based assays useful for interrogating their 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.

VI. CLAIM CONSTRUCTION

55. 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.

56. 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.

⁵⁰ See Section IV.

VII. BACKGROUND

A. Hormone Biochemistry Foundation

57. Peptides are short strings of at least two amino acids linked by covalent peptide bonds.⁵¹ Both natural and engineered peptides can trigger a signaling pathway by interacting with the receptor for that signaling pathway.⁵² Some signaling peptide ligands act as peptide hormones.⁵³

1) Proteinogenic Amino Acids

58. Proteins in the body are naturally formed using 20 common amino acids as building blocks. Two additional amino acids, selenocysteine and pyrrolysine, can also be incorporated by the ribosome using additional translation

⁵¹ Fields G. B. Introduction to peptide synthesis. *Current protocols in protein science, Chapter 18*, **2002**; 18.1.1–18.1.9 (hereinafter “Fields,” EX1011). Fields published in 2002 in *Current protocols in protein science*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1011, 18.1.1.

⁵² Nelson, D. L., *et al.*, Chapters 4-5, 7, *LEHNINGER PRINCIPLES OF BIOCHEMISTRY*, 3rd ed. (eds. Ryan, M., *et al.*, Worth Publishers) **2000** (hereinafter “Nelson,” EX1014). Nelson published in 2000 in *LEHNINGER PRINCIPLES OF BIOCHEMISTRY*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1014, 118-119, 203, Fig. 5-5.

⁵³ Segaloff, D. L., *et al.*, Chapter 9: Internalization of Peptide Hormones and Hormone Receptors, *Hormones and their Actions, Part I*, (eds. Cooke, B. A., *et al.*, Elsevier) **1988**, 133-149 (hereinafter “Segaloff,” EX1015). Segaloff published in 1988 in *Hormones and their Actions, Part I*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. *See generally* EX1015.

factors and specific transfer RNAs.⁵⁴ Figure 1 below shows the chemical structures of these amino acids as reproduced under a different figure number in a prior art reference.⁵⁵ The “unshaded portions are those common to all the amino acids” (the backbone) while the shaded portions indicate the side chains of the amino acids that can differentiate them.⁵⁶ It is commonly known that the 20 proteogenic amino acids are in the L-configuration. For clarity, Figure 17 (provided in Appendix I below) further provides structures of these amino acids explicitly showing their stereochemistry.

⁵⁴ Zhang Y., Baranov P.V., Atkins J.F., Gladyshev V.N. Pyrrolysine and selenocysteine use dissimilar decoding strategies. *J Biol Chem.* **2005** May 27;280(21):20740-51 (hereinafter “Zhang,” EX1016). Zhang published in 2005 in the peer-reviewed periodical *Journal of Biological Chemistry*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1016, Abstract.

⁵⁵ EX1014, 119, Fig. 5-5.

⁵⁶ *Id.*

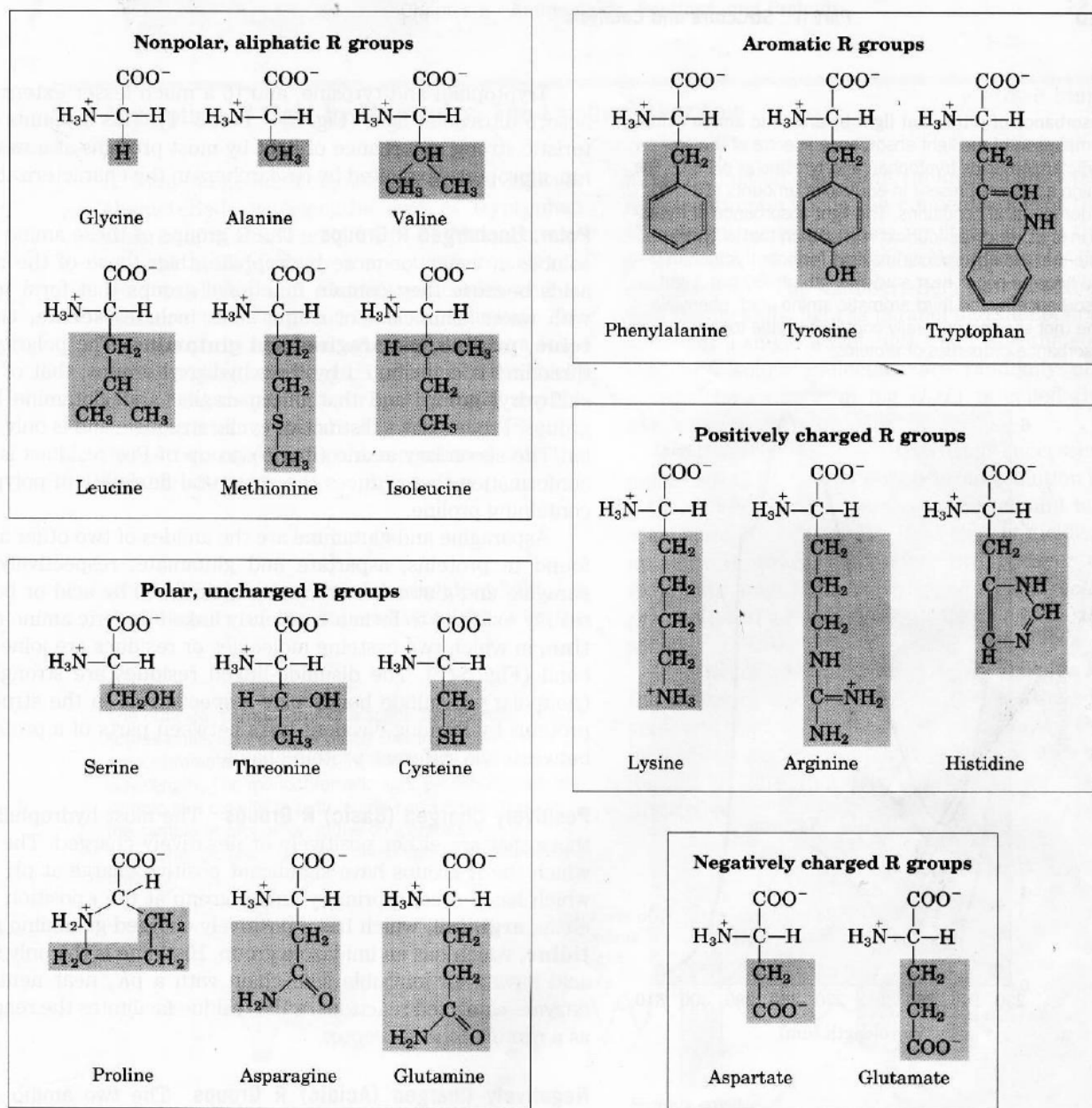


Figure 1.

59. These amino acid residues were regularly described using a three letter code or a one letter code,⁵⁷ as illustrated in this chart:

⁵⁷ EX1014, 118, Table 5-1.

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

60. The side chains of the amino acids can alter the chemical characteristics of different amino acids, sometimes impacting the function of the amino acid. For example, asparagine (Asn, N) and glutamic acid (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).⁵⁸ In some circumstances, these differences can impact the function of a peptide significantly. Where these two amino acid residues are highly interchangeable for a

⁵⁸ EX1014, 118-120.

given peptide function, that is a strong indication that the function of the peptide permits employing another amino acid residue with consistent side chain structure and functional group, and with conserved functional activity (e.g., charge, hydrophobicity, etc.).

2) Peptide Synthesis

61. Synthesis of peptides has been described as early as 1901,⁵⁹ however, synthesis at this stage was rudimentary and time consuming. In 1963, Robert Bruce Merrifield published his first solid-phase peptide synthesis (SPPS) then of a tetramer.⁶⁰ 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

⁵⁹ EX1011, 18.1.1.

⁶⁰ Merrifield R. B. Solid phase peptide synthesis. I. The synthesis of a tetrapeptide. *J. Am. Chem. Soc.* **1963**;85:2149–2154. (hereinafter “Merrifield,” EX1018). Merrifield published in 1963 in the peer-reviewed periodical *Journal of the American Chemical Society*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Merrifield marks the establishment of the method of solid phase peptide synthesis and is a reference within the same field at issue that is reasonably pertinent to the issues addressed. EX1018, Abstract.

for therapeutic applications. 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.

62. SPPS utilizes a solid support (a polymer resin) to provide protection for the C-terminus of the first amino acid with Boc or Fmoc protecting groups. After the addition of an amino acid, the protection group is removed, the resin is washed, and the process is repeated until the desired peptide sequence has been achieved. The completed peptide can then be cleaved from the resin.⁶¹

3) Synthetic Analogues of Peptides as Drugs

63. Since the 1980s, skilled artisans have been producing synthetic analogues of naturally occurring peptide hormones to improve stability, effectiveness, and half-life of peptide therapeutics. Breakthroughs in the synthesis

⁶¹ *Id.*

of hormone mimetics such as oxytocin⁶² and insulin⁶³ further highlighted the potential of peptide hormones as therapeutics.

64. Developing synthetic analogues of peptide hormones as drugs was a well-established and conventional practice by 2015. Skilled artisans responded to the discovery of the naturally occurring 10-residue peptide hormone for Gonadotropin-Releasing Hormone (GnRH) with the immediate development of abundant synthetic analogues. “The physiological and therapeutic importance attributed to the discovery of the new substance [GnRH] was greatly increased by the prospect of the design of potent and long-acting GnRH agonists and

⁶² Sawyer, W. H. & Manning, M. Synthetic analogs of oxytocin and the vasopressins. *Annu Rev. Pharm.* **1973**;13, 1–17, (hereinafter “Sawyer,” EX1019). Sawyer published in 1973 in the peer-reviewed periodical *Annual Review of Pharmacology and Toxicology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Sawyer describes the synthesis of hormone peptide analogs for therapeutic use. The reference is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1019, 6551.

⁶³ Keen, H. et al. Human insulin produced by recombinant DNA technology: safety and hypoglycaemic potency in healthy men. *Lancet* **1980**;2, 398–401, (hereinafter “Keen,” EX1020). Keen published in 1980 in the peer-reviewed periodical *Lancet*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Keen established that recombinant insulin peptide was a safe and efficacious alternative to native peptide, and is a reference within the same field at issue that is reasonably pertinent to the issues addressed. EX1020, 398.

antagonists.”⁶⁴ The discovery of the natural protein was followed by skilled artisans making over 2000 analogues of GnRH. *Id.* For GnRH, these efforts were directed to “more potent and longer acting analogs” which “were thought to be necessary for practical clinical utility.”⁶⁵

65. 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. This approach was known to result in undesirable

⁶⁴ Karten M.J., Rivier J.E. Gonadotropin-releasing hormone analog design. Structure-function studies toward the development of agonists and antagonists: rationale and perspective. *Endocr Rev.* **1986** Feb;7(1):44-66, (hereinafter “Karten,” EX1021). Karten published in 1986 in the peer-reviewed periodical *Endocrinology Reviews*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1021, 44.

⁶⁵ *Id.*, 45.

immunogenicity.⁶⁶ A more desirable approach involved conjugation of the peptide to a lipophilic moiety.⁶⁷

⁶⁶ Garay R.P., El-Gewely R., Armstrong J.K, Garratty G., Richette P. Antibodies against polyethylene glycol in healthy subjects and in patients treated with PEG-conjugated agents. *Expert Opin Drug Deliv.* **2012** Nov;9(11):1319-23 (hereinafter “Garay,” EX1022). Garay published in 2012 in the peer-reviewed periodical *Expert Opinions in Drug Delivery*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Garay describes that up to 25% of healthy blood donors (*i.e.* no indication of knowingly treated with a PEGylated drug), and up to 89% of patients treated with PEGylated drug (*e.g.* Pegloticase) have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds. EX1022, Abstract, 1320.

⁶⁷ Knudsen L.B. Liraglutide: the therapeutic promise from animal models. *Int J Clin Pract Suppl.* **2010** Oct;(167):4-11. (Addition of fatty acid chains to Lys²⁰ of liraglutide promotes reversible binding of peptide to albumin in the blood, decreasing degradation by DPP-IV and protracting circulation and therapeutic effect), (hereinafter “Knudsen,” EX1023). Knudsen published in the peer-reviewed periodical *International Journal of Clinical Practice, Supplement* in 2010, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1023, 5; Ward B.P., Ottaway N.L., Perez-Tilve D., Ma D., Gelfanov V.M., Tschöp M.H., Dimarchi R.D. Peptide lipidation stabilizes structure to enhance biological function. *Mol Metab.* **2013** Sep 5;2(4):468-79, (hereinafter “Ward,” EX1024). Ward published in the peer-reviewed periodical *Molecular Metabolism* in 2013, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Ward describes “site-specific lipidation alone could generate balanced, high potency co-agonism in glucagon-based peptides.” EX1024, 475; Zhang L., Bulaj G. Converting peptides into drug leads by lipidation. *Curr Med Chem.* **2012**;19(11):1602-18, (hereinafter “Zhang,” EX1025). Zhang published in the peer-reviewed periodical *Current Medicinal Chemistry* in 2012, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Zhang describes that lipidation is commonly employed to improve metabolic stability, membrane permeability, and bioavailability of peptide drugs. EX1025, Abstract.

4) Large-Scale Peptide Synthesis and Screening

66. By 2015, it was common to construct libraries of tens of thousands of peptides as part of drug discovery efforts so that the pharmaceutical properties of the active analogues could be evaluated. In 2013, for example, Krausen et al. constructed a *de novo* combinatorial peptide library of 16,200 peptides of 24-26 residues each, wherein 6 residues of each peptide were varied to screen the peptides for self-assembly properties.⁶⁸ Krausen et al. identified 16 pore-forming peptides (~0.2% of the total library).⁶⁹ This study highlighted that the production and testing of tens of thousands of peptides was both a feasible and productive endeavor by those of skill in the art, and was successfully used at the relevant time to identify useful peptide sequences for further study and potential development.

67. Methods to synthesize large-scale peptide libraries had been largely established by 2015, including the “one-bead, one-peptide” or “one-bead, one-compound” method of library production.⁷⁰ As stated by Lam et al., this “simple

⁶⁸ Krausen A.J., He J., Wimley A.W., Hoffmann A.R., Wimley W.C. Synthetic molecular evolution of pore-forming peptides by iterative combinatorial library screening. *ACS Chem Biol.* **2013** Apr 19;8(4):823-31, (hereinafter “Krausen,” EX1026). Krausen published in 2013 in the peer-reviewed periodical *ACS Chemical Biology*, and is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1026, Abstract, 824-826.

⁶⁹ *Id.*

⁷⁰ Lam K.S., Salmon S.E., Hersh E.M., Hruby V.J., Kazmierski W.M., Knapp R.J. A new type of synthetic peptide library for identifying ligand-binding activity.

methodology greatly enhances the production and rapid evaluation of random libraries of millions of peptides so that acceptor-binding ligands of high affinity can be rapidly identified and sequenced.”⁷¹ By the critical date, technology based around the “one-bead, one-peptide” method had evolved to synthesize and screen libraries of more than 1 million members in a matter of weeks.⁷² Identification of screening hits had also evolved. Liu et al. notes “Others and we have previously reported partial Edman degradation/mass spectrometry (PED/MS) as a high-throughput peptide (or peptoid) sequencing technique and have applied it to sequence >30,000 peptides/year in our laboratory.”⁷³ This rapid technology advancement and increased throughput of peptide-based screens allowed the

Nature. **1991** Nov 7;354(6348):82-4., (hereinafter “Lam,” EX1027). Lam published in 1991 in the peer-reviewed periodical *Nature*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Lam established a systematic screening approach for analyzing large quantities of peptides. EX1027, 82-83.

⁷¹ *Id.*

⁷² Liu T., Qian Z., Xiao Q., Pei D. High-throughput screening of one-bead-one-compound libraries: identification of cyclic peptidyl inhibitors against calcineurin/NFAT interaction. *ACS Comb Sci*. **2011** Sep 12;13(5):537-46, (hereinafter “Liu,” EX1028). Liu published in 2011 in the peer-reviewed periodical *ACS Combinatorial Sciences*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Liu integrates technical advances in peptide analysis with one-bead, one-peptide screening approaches to screen large quantities of peptides. EX1028, 540-542.

⁷³ *Id.*

skilled artisan to modify and iterate on peptide sequences of interest at a large scale.⁷⁴ Because of the advanced state of the art of peptide synthesis, a POSA was eager, not reluctant, to synthesize new peptides and to measure their activities and pharmaceutical properties.

B. Peptide Hormones and G-Protein Coupled Receptors (GPCR)

68. As introduced above, the body uses peptide hormones that bind peptide-based receptors to trigger signaling pathways and thereby regulate activities in the body. For example, a peptide hormone may bind to the extracellular portion of a protein structure that extends through a membrane (membrane-bound protein). This binding interaction may change the shape (conformation) of the membrane-bound protein, thus changing the way the intracellular portion of the membrane-bound protein interacts with other proteins within the cell, for example. In this way, the body uses peptides to generate signaling cascades to activate (agonist hormones) or deactivate (antagonist hormones) functions within the body.

69. G Protein-Coupled Receptors (GPCRs) are transmembrane proteins that comprise the largest and most diverse group of receptors in eukaryotes.⁷⁵

⁷⁴ *Id.*, 541-543.

⁷⁵ Tautermann C.S. GPCR structures in drug design, emerging opportunities with new structures. *Bioorg Med Chem Lett.* **2014** Sep 1;24(17):4073-9, (hereinafter “Tautermann,” EX1029). Tautermann published in 2014 in the peer-reviewed periodical *Bioorganic & Medicinal Chemistry Letters*, is a reference within the

GPCRs aid in critical cellular functions through signal transduction from the cell exterior to the cytosol via induction of signaling cascades within the cytosol.⁷⁶ Given their wide range of biological functions and diverse expression patterns across tissues, GPCRs have been highly sought after as drug targets for a range of indications including cancer, diabetes, and neurodegenerative diseases. By 2015, it was estimated that about 50% of all modern drugs acted on a receptor within the GPCR superfamily.⁷⁷

70. GPCRs generally operate when the signaling ligand binds on the extracellular face of the receptor, stabilizing conformations of the GPCR that interact with different affinities to downstream signaling molecules and initiate signaling cascades.⁷⁸ Activation of signaling can occur through G protein pathways and arrestins (β -arrestin-1 and -2), with some receptor-ligand systems

same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1029, 4073.

⁷⁶ *Id.*, 4073.

⁷⁷ *Id.*, 4073.

⁷⁸ Donnelly D. The structure and function of the glucagon-like peptide-1 receptor and its ligands. *Br J Pharmacol.* **2012** May;166(1):27-41, (hereinafter “Donnelly,” EX1030). Donnelly published in 2012 in the peer-reviewed periodical *British Journal of Pharmacology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Donnelly discusses the structure-activity relationship of GLP-1 and summarizes GLP-1 receptor interactions, and is a reference within the same field at issue and should therefore be considered as prior art to the challenged patent. EX1030, 32.

preferentially signaling through one or the other in a biased manner.⁷⁹ For example, incretin (insulin-promoting) properties of GLP-1R and GIPR signaling were believed to result at least in part from G-protein initiated cyclic AMP (cAMP) production.⁸⁰

71. However, β -arrestins were also known to play a role in GLP-1R and GIPR signaling. For example, it was known that GPCR-ligand-mediated phosphorylation of the receptor allows β -arrestins to bind to the phosphorylated

⁷⁹ Rajagopal, S., Rajagopal, K., & Lefkowitz, R. J. Teaching old receptors new tricks: biasing seven-transmembrane receptors. *Nature Reviews. Drug Discovery*, **2010**;9(5), 373–386, (hereinafter “Rajagopal,” EX1031). Rajagopal published in 2010 in peer-reviewed periodical *Nature Reviews. Drug Discovery*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1031, 373-375.

⁸⁰ Yu Z., Jin T. New insights into the role of cAMP in the production and function of the incretin hormone glucagon-like peptide-1 (GLP-1). *Cell Signal.* **2010** Jan;22(1):1-8. doi: 10.1016/j.cellsig.2009.09.032, (hereinafter “Yu,” EX1032). Yu published in 2010 in peer-reviewed periodical *Cell Signaling*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1032, 1,6.

GPCR C-terminus.⁸¹ The GPCR is then desensitized and internalized.⁸² Studies showed that GLP-1-induced activation of GLP-1R can result in recruitment of β -arrestin,⁸³ however, the GLP-1 receptor can also be differentially activated with peptide hormones such as oxyntomodulin.⁸⁴ Jorgensen et al. revealed that while oxyntomodulin and glucagon were full agonists in GLP1R-mediated cyclic cAMP signaling, the peptides were partial agonists in recruitment of β -arrestins,

⁸¹ Roed S.N., Nøhr A.C., Wismann P., Iversen H., Bräuner-Osborne H., Knudsen S.M., Waldhoer M. Functional consequences of glucagon-like peptide-1 receptor cross-talk and trafficking. *J Biol Chem.* **2015** Jan 9;290(2):1233-43 (published online December 1, 2014), (hereinafter “Roed,” EX1033). Roed et al. describes the structure-activity relationship of GLP-1, GIP, and glucagon receptors as GPCRs. Roed published online on December 1, 2014 in the peer-reviewed periodical *Journal of Biological Chemistry*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1033, 1236.

⁸² *Id.*, 1233.

⁸³ Jorgensen R., Norklit Roed S., Heding A., Elling C. E. Beta-arrestin-2 as a competitor for GRK2 interaction with the GLP-1 receptor upon receptor activation. *Pharmacology.* **2011**;88, 174–18, hereinafter “Jorgensen 2011,” EX1034). Jorgensen et al. published in 2011 in the peer-reviewed periodical *Pharmacology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1034, Abstract, 148-149.

⁸⁴ Jorgensen R., Kubale V., Vrecl M., Schwartz T.W., Elling C.E. Oxyntomodulin differentially affects glucagon-like peptide-1 receptor beta-arrestin recruitment and signaling through Galpha(s). *J Pharmacol Exp Ther.* **2007** Jul;322(1):148-54, (hereinafter “Jorgensen 2007,” EX1035). Jorgensen published in 2007 in the peer-reviewed periodical *Journal of Pharmacology and Experimental Therapeutics*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1035, 151-152.

highlighting a biased agonism phenomenon of GLP1R receptor signaling that was dependent on the peptide ligand.⁸⁵ Following this study, Sonoda et al. discovered that β -arrestin-1 knockdown reduced GLP-1 insulin secretion through a cAMP-dependent pathway.⁸⁶

72. 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.^{87,88} Class B GPCR signaling was understood by 2015 to be initiated by a two-step signaling process involving two separate domains of the

⁸⁵ *Id.*, 151-152.

⁸⁶ Sonoda N, Imamura T., Yoshizaki T., Babendure J.L., Lu J.C., Olefsky J.M. Beta-Arrestin-1 mediates glucagon-like peptide-1 signaling to insulin secretion in cultured pancreatic beta cells. *Proc Natl Acad Sci U S A*. **2008** May 6;105(18):6614-9, (hereinafter “Sonoda,” EX1036). Sonoda published in 2008 in the peer-reviewed periodical *Proceedings of the National Academy of Science*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Sonoda describes the role of beta-arrestin-1 in GLP-1 receptor signaling. EX1036, 6616.

⁸⁷ EX1030 (Donnelly), 27.

⁸⁸ Siu F.Y., He M., de Graaf C., Han G.W., Yang D., Zhang Z., Zhou C., Xu Q., Wacker D., Joseph J.S., Liu W., Lau J., Cherezov V., Katritch V., Wang M.W., Stevens R.C. Structure of the human glucagon class B G-protein-coupled receptor. *Nature*. **2013** Jul 25;499(7459):444-9, (hereinafter “Siu,” EX1037). Siu published in 2013 in the peer-reviewed periodical *Nature*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Siu reported the first crystal structure of the human glucagon receptor. EX1037, 444.

receptor (“two-domain model”).⁸⁹ 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.^{90,91}

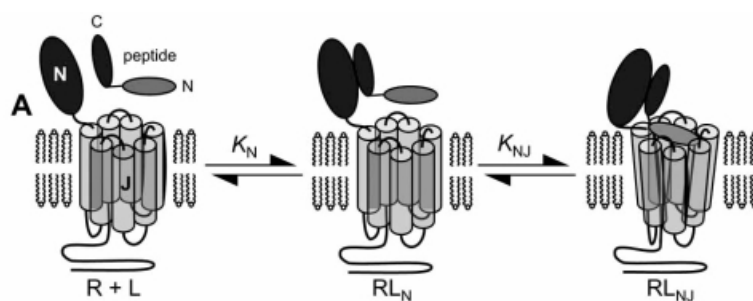


Figure 2. Adapted from Hoare S. R. (2007). Allosteric modulators of class B G-protein-coupled receptors. *Current neuropharmacology*, 5(3), 168–179⁹². “Two domain model of peptide interaction with Class B GPCR’s. A. Schematic representation of the two-domain model. The carboxyl-terminal portion of the peptide binds the extracellular N-terminal

⁸⁹ EX1030 (Donnelly), 28.

⁹⁰ Hoare S.R. Mechanisms of peptide and nonpeptide ligand binding to Class B G-protein-coupled receptors. *Drug Discov Today*. **2005** Mar 15;10(6):417-27, (hereinafter “Hoare 2005,” EX1038). Hoare 2005 published in 2005 in the peer-reviewed periodical *Drug Discovery Today*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1038, 419-420.

⁹¹ EX1030 (Donnelly), 28.

⁹² Hoare S. R. Allosteric modulators of class B G-protein-coupled receptors. *Current Neuropharmacology*. **2007**;5(3), 168–179, (hereinafter “Hoare 2007,” EX1039). Hoare 2007 published in 2007 in the peer-reviewed periodical *Current Neuropharmacology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1039, 170.

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 ratio.”

1) Incretin GCPR Ligands

73. Glucose-dependent insulintropic polypeptide (GIP, also called gastric inhibitory peptide) and Glucagon-like Peptide (GLP)-1 are both incretins (insulin-promoting hormones) that exist naturally in the body.⁹³ The body is designed to release them postprandially, among other things, to convey satiety.⁹⁴ For example, incretin properties of GLP-1R and GIPR signaling were believed to result at least in part from G-protein initiated cAMP production.⁹⁵

⁹³ Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: Similarities and differences. *J Diabetes Investig.* 2010 Apr 22;1(1-2):8-23, (hereinafter “Seino,” EX1040). Seino published in 2010 in the periodical *Journal of Diabetes Investigation*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Seino describes the function of the GIP and GLP peptides and their receptors GLP-1R and GIPR. EX1040, 8-9.

⁹⁴ *Id.*, 8-9.

⁹⁵ *Id.*, 11.

74. GIP was first discovered in 1989 for its ability to inhibit gastric secretion.^{96,97} The 42-amino acid peptide was later found to stimulate pancreatic insulin secretion in healthy human volunteers⁹⁸ by stimulating pancreatic beta cells.⁹⁹ With the stimulation of insulin release, GIP was able to improve glucose

⁹⁶ Brown J.C., Mutt V., Pederson R.A. Further purification of a polypeptide demonstrating enterogastrone activity. *J Physiol* **1970**; 209: 57–64, (hereinafter “Brown,” EX1041). Brown published in 1970 in the peer-reviewed periodical *Journal of Physiology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. *See generally* EX1041.

⁹⁷ Inagaki, N., Seino Y., Takeda J., *et al.* Gastric inhibitory polypeptide: Structure and chromosomal localization of the human gene. *Mol Endocrinol* **1989**; 3: 1014–1021, (hereinafter “Inagaki,” EX1042). Inagaki *et al.* published in 1989 in the peer-reviewed periodical *Molecular Endocrinology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Inagaki describes the structure and function of the GIP peptide. EX1042, 1014, 1016-1017.

⁹⁸ Dupre J., Ross S.A., Watson D., *et al.* Stimulation of insulin secretion by gastric inhibitory polypeptide in man. *J Clin Endocrinol Metab* **1973**; 37: 826–828, (hereinafter “Dupre,” EX1043) Dupre published in 1973 in the peer-reviewed periodical *The Journal of Clinical Endocrinology and Metabolism*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Dupre describes the function of GIP peptide in relation to insulin secretion. EX1043, Abstract.

⁹⁹ Adrian T.E., Bloom S.R., Hermansen K., *et al.* Pancreatic polypeptide, glucagon and insulin secretion from the isolated perfused canine pancreas. *Diabetologia* **1978**; 14: 413–417, (hereinafter “Adrian,” EX1044). Adrian published in 1978 in the peer-reviewed periodical *Diabetologia*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1044, 414.

tolerance and improve physiological response to high blood sugar,¹⁰⁰ providing a potential mechanism for control of hyperglycemia.

75. Discovery of a 37-amino acid Glucagon-like peptide-1 (GLP-1) hormone was made by Joel Habener and Svetlana Mojsov.¹⁰¹ The peptide stimulated insulin secretion and suppressed glucagon secretion to regulate blood sugar levels. *Id.* GLP-1(1-37) is expressed in intestinal L cells and is derived from cell-specific post-translational processing of the preproglucagon gene.¹⁰²

76. In 1987, Mosjov et al. and others discovered that the 37-residue 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).¹⁰³ In fact, two N-terminally truncated products (GLP-1(7-37) and GLP-1(7-36) amide) are the active species *in vivo*, are equipotent to one another, are the major physiological incretin in humans, and are commonly

¹⁰⁰ EX1043 (Dupre), Abstract.

¹⁰¹ Lund P.K., Goodman R.H., Dee P.C., Habener J.F. Pancreatic preproglucagon cDNA contains two glucagon-related coding sequences arranged in tandem. *Proc Natl Acad Sci U S A.* **1982** Jan;79(2):345-9, (hereinafter “Lund,” EX1045). Lund published in 1982 in the peer-reviewed periodical *Proceedings of the National Academy of Sciences*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Lund identified the GLP-1 peptide by immunoprecipitation. *See generally* EX1045.

¹⁰² EX1030 (Donnelly), 27.

¹⁰³ *Id.*

referred to as the endogenous form of GLP-1.¹⁰⁴ 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.¹⁰⁵

77. Limitations on the use of endogenous GLP-1 for the treatment of diabetes and obesity were recognized in the form of short half-life (mere minutes) and 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).^{106,107} Though some forms of endogenous peptide cleavage activate GLP-1

¹⁰⁴ EX1030 (Donnelly), 27.

¹⁰⁵ EX1030 (Donnelly), 27-28.

¹⁰⁶ EX1030 (Donnelly), 28.

¹⁰⁷ Hui H., Farilla L., Merkel P., Perfetti R. The short half-life of glucagon-like peptide-1 in plasma does not reflect its long-lasting beneficial effects. *Eur J Endocrinol.* **2002** Jun;146(6):863-9, (hereinafter “Hui,” EX1046). Hui published in 2002 in the peer-reviewed periodical *European Journal of Endocrinology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1046, Abstract.

(i.e., cleaving N-terminal residues 1-6 of the pro-peptide), other forms essentially deactivate it. In particular, studies identified dipeptidyl peptidase (DPP)-IV cleavage site at pro-peptide residue 8 (Ala), where active GLP-1 was cleaved into GLP-1(9-37) or GLP-1(9-36)amide,¹⁰⁸ a much less active form with lower affinity for the GLP-1 receptor.^{109,110,111} In parallel, Kieffer et al. demonstrated the absence

¹⁰⁸ The numbering in GLP-1(9-37) and GLP-1(9-36) refers to the positions in the pro-peptide.

¹⁰⁹ Singh A. K. Dipeptidyl peptidase-4 inhibitors: Novel mechanism of actions. *Indian journal of endocrinology and metabolism*, **2014**;18(6), 753–759 (hereinafter “Singh,” EX1047). Singh published in 2014 in the peer-reviewed periodical *Indian journal of endocrinology and metabolism*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1047, 753-754.

¹¹⁰ Kieffer T.J., McIntosh C.H.S., Pederson R.A. Degradation of glucose-dependent insulintropic polypeptide (GIP) and truncated glucagon-like peptide-1 (tGLP-1) *in vitro* and *in vivo* by dipeptidyl peptidase IV (DDP IV). *Endocrinology* **1995**; 136: 3585–36596, (hereinafter “Kieffer,” EX1048). Kieffer published in 1995 in the peer-reviewed periodical *Endocrinology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Kieffer established modified GLP-1 peptides that were resistant to DPP-IV degradation and demonstrated improved half-life *in vivo*. EX1048, 3587, Figure 1.

¹¹¹ Montrose-Rafizadeh C., Yang H., Rodgers B.D., Beday A., Pritchette L.A., Eng J. High potency antagonists of the pancreatic glucagon-like peptide-1 receptor. *J Biol Chem.* **1997**;272:21201–21206, (hereinafter “Montrose-Rafizadeh,” EX1049). Montrose-Rafizadeh published in 1997 in the peer-reviewed periodical *Journal of Biological Chemistry*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Montrose-Rafizadeh describes truncation at the N-terminus (resulting in GLP-1(9-39)) led to a 94-fold decrease in affinity and yielded about 50% of maximum agonist activity. EX1049, 21204, Table I.

of both GLP-1 and GIP degradation and improved GIP/GLP-1 activity in DPP-IV deficient rodents.¹¹² 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) for therapeutic use in diabetes, obesity, and cardiovascular health.

2) Diabetes and Obesity Treatment Using GLP-1 and Dual GLP-1/GCPR Agonists

78. In the 1980's researchers studying why Gila monsters eat very rarely discovered the endogenous GLP-1-receptor agonist exendin-4, which was resistant to DPP-IV cleavage largely because the Ala² was replaced with a DPP-IV resistant amino acid (Gly).¹¹³

79. Subsequently, the synthetic GLP-1 agonist liraglutide^{114, 115} was engineered to have 97% homology to the active portion of endogenous GLP-1 (7-

¹¹² EX1048 (Kieffer), 3587, Figure 1.

¹¹³ EX1030 (Donnelly), 28.

¹¹⁴ VICTOZA (liraglutide) injection ("VICTOZA") (EX1050) is a drug label that was approved by the FDA in January 2010. It is prior art that was publicly available before the earliest possible priority date of January 5, 2015. EX1050 was obtained directly from the FDA website by selecting the label corresponding to the approval date of January 25, 2010. EX1050, 1, 11.

¹¹⁵ SAXENDA (liraglutide) injection ("SAXENDA") (EX1013) is a drug label that was approved by the FDA in December 2014. It is prior art that was publicly available before the earliest possible priority date of January 5, 2015. EX1013 was obtained directly from the FDA website by selecting the label corresponding to the approval date of December 23, 2014. EX1013, 1, 14.

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).¹¹⁶ Liraglutide is made by attaching a C-16 fatty acid (palmitic acid) to the peptide with a γ -glutamic (γ Glu) acid spacer at the epsilon-amino group of the lysine at aligned position 20 (pro-peptide position 26) of the peptide to increase its half-life. Liraglutide had a half-life of 13 hours, and was administered as a once-daily injection.^{117, 118}

¹¹⁶ Bode B. Liraglutide: a review of the first once-daily GLP-1 receptor agonist. *Am J Manag Care*. **2011** Mar;17(2 Suppl):S59-70, (hereinafter “Bode” EX1051). Bode published in 2011 in the peer-reviewed periodical *American Journal of Managed Care*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1051, Abstract, S59; EX1050, 1, 11-12.

¹¹⁷ Neumiller JJ, Campbell RK. Liraglutide: a once-daily incretin mimetic for the treatment of type 2 diabetes mellitus. *Ann Pharmacother*. **2009** Sep;43(9):1433-44. (hereinafter “Neumiller” EX1052). Neumiller published in 2009 in the peer-reviewed periodical *Annals of Pharmacotherapy*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1052, 1435.

¹¹⁸ EX1013 (SAXENDA), 1, 14-15; EX1050 (VICTOZA), 1, 11-12.

80. The peptide sequences of the active endogenous GIP and GLP-1 peptides are shown below in alignment with exenatide^{119,120} and liraglutide¹²¹. Amino acid residues are color-coded in green that are conserved across all four peptides. Different shades of blue are used to identify residues appearing in the endogenous GIP (GIPR agonist), GLP-1 (GLP-1R agonist) or exenatide (GLP-1R agonist) sequence.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
GIP	Y	A	E	G	T	F	I	S	D	V	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q
GLP-1	N	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R	G	NH2										
Liraglutide	N	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K*	E	F	I	A	W	L	V	R	G	R	G											
Exenatide	N	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2			

81. FDA approved dulaglutide as a once-weekly injection in 2014.¹²² For dulaglutide, the two identical copies of an N-terminal GLP-1 analogue sequence linked to the Fc portion of a modified human IgG₄ heavy chain by a small peptide

¹¹⁹ BYDUREON (exenatide) injection (“BYDUREON”) (EX1053) is a drug label that was approved by the FDA in January 2012. It is prior art that was publicly available before the earliest possible priority date of January 5, 2015. EX1053 was obtained directly from the FDA website by selecting the label corresponding to the approval date of January 27, 2012. EX1053, 1, 16.

¹²⁰ BYETTA (exenatide) injection (“BYETTA”) (EX1054) is a drug label that was approved by the FDA in April 2005. It is prior art that was publicly available before the earliest possible priority date of January 5, 2015. EX1054 was obtained directly from the FDA website by selecting the label corresponding to the approval date of April 5, 2005. EX1054, 1-2.

¹²¹ EX1013 (SAXENDA), 1, 14-15; EX1050 (VICTOZA), 1, 11-12.

¹²² TRULICITY (dulaglutide) injection (“TRULICITY”) (EX1055) is a drug label that was approved by the FDA in September 2014. It is prior art that was publicly available before the earliest possible priority date of January 5, 2015. EX1055 was obtained directly from the FDA website by selecting the label corresponding to the approval date of September 18, 2014. EX1055, 1-2.

linker were fused together using a disulfide linker. The increased size of the fusion protein as compared to the individual peptide helped increase the half-life sufficiently to employ once-weekly dosing. The GLP-1 peptide portion of the fusion protein shares 90% homology to active native human GLP-1 (7-37), indicating there were three amino acid substitutions as compared to the native peptide. Structural modifications were directed to reducing deactivation of the peptides by endogenous DPP-IV enzyme and to reducing immunogenicity.

82. Though lixisenatide¹²³ (derived from exendin-4) and semaglutide¹²⁴ first received FDA approval for diabetes after the January 2015 priority date, they were discussed in the literature before the critical date.¹²⁵ Indeed, it was known by

¹²³ ADLYXIN (lixisenatide) injection (“ADLYXIN”) (EX1056) is a drug label that was approved by the FDA in July 2016. EX1056, 1-2, 11. EX1056 was obtained directly from the FDA website by selecting the label corresponding to the approval date of July 27, 2016.

¹²⁴ OZEMPIC (semaglutide) injection (“OZEMPIC”) (EX1057), is a drug label that was approved by the FDA in December 2017. EX1057, 1,3, 11. EX1057 was obtained directly from the FDA website by selecting the label corresponding to the approval date of December 5, 2017.

¹²⁵ Monami M., Dicembrini I., Marchionni N., Rotella C.M., Mannucci E. Effects of glucagon-like peptide-1 receptor agonists on body weight: a meta-analysis. *Exp Diabetes Res.* **2012**;2012:672658, (hereinafter “Monami,” EX1058). Monami published in 2012 in the peer-reviewed periodical *Experimental Diabetes Research*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Monami discusses a meta-analysis of the ability of GLP-1 agonists to reduce weight in obese patients. EX1058, Abstract, 2.

December 2014 that semaglutide was a GLP-1 derivative for once-weekly administration that was under development by Novo Nordisk A/S.¹²⁶

83. Before 2015, once-weekly administration of GLP-1 agonists with dual agonist activity were known to eliminate obesity. For example, once-weekly administration of GLP-1/glucagon receptor co-agonists was shown by 2009 to normalize glucose tolerance and reverse obesity in mice by reducing food intake and increasing energy expenditure without any overt adverse effects.¹²⁷ As mentioned above, glucagon also is a Class B GCPR agonist, like GIP and GLP-1. Glucagon receptor signaling has some effect in decreasing insulin secretion (opposite to GLP-1 and GIP), but also induces satiety while increasing energy expenditure.¹²⁸ Accordingly, GLP-1/glucagon receptor dual-agonisms was understood potentially to be beneficial for treating diabetes and obesity by

¹²⁶ See, e.g., EX1010, 1:21-23; EX1009, Example 4.

¹²⁷ Day J.W., Ottaway N., Patterson J.T., *et al.* A new glucagon and GLP-1 co-agonist eliminates obesity in rodents. *Nat Chem Biol.* **2009** Oct;5(10):749-57, (hereinafter “Day,” EX1059). Day published in 2009 in the peer-reviewed periodical *Nature Chemical Biology*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1059, 754, Figure 5-6; Pocai A., Carrington P.E., Adams J.R., *et al.* Glucagon-like peptide 1/glucagon receptor dual agonism reverses obesity in mice. *Diabetes.* **2009** Oct;58(10):2258-66, (hereinafter “Pocai,” EX1060). Pocai published in 2009 in the peer-reviewed periodical *Diabetes*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1060, 2261, Figure 2.

¹²⁸ *Id.*

decreasing food consumption and increasing energy expenditure despite their partially-offsetting insulin secretion effects, particularly where obesity was driving insulin resistance.

84. By 2013, the literature reported that GLP-1/GIP receptor co-agonists demonstrated enhanced antihyperglycemic, insulinotropic, and weight lowering efficacy relative to selective GLP-1 agonists in rodents, monkeys, and humans while avoiding adverse gastrointestinal effects that typify selective GLP-1 agonists.¹²⁹ By 2015, both GLP-1 and GIP peptides were being explored, both *in vitro* and *in vivo*.^{130,131} Notably, a dual incretin GLP-1/GIP agonist exhibited “enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists.”¹³² The duration of action of the dual agonists was refined through site-specific lipidation to support less frequent administration.¹³³ Accordingly, it was

¹²⁹ Finan B., Ma T., Ottaway N., *et al.* Unimolecular dual incretins maximize metabolic benefits in rodents, monkeys, and humans. *Sci Transl Med.* **2013** Oct 30;5(209):209ra151, (hereinafter “Finan,” EX1061). Finan published in 2013 in the peer-reviewed periodical *Science Translational Medicine*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Finan describes a dual incretin that could act equally on both the GLP-1 and GIP receptors *in vivo*. EX1061, 10-11.

¹³⁰ EX1059 (Day), 754, Figure 5-6.

¹³¹ *See generally* EX1061 (Finan).

¹³² *Id.*, Abstract, 1.

¹³³ *Id.*, Abstract, 1.

obvious by January 2015 to use site-specific lipidation of GLP-1 agonists and dual agonists to achieve once-weekly dosing.

C. Rational Design of Incretin Agonists

85. By 2015, the state of the art permitted the rational design of GLP-1 agonists and dual agonists. This was possible because much was known about the structure and function of GLP-1R and its natural ligand GLP-1, including many of the key amino acid residues of the peptide and the sites to which they bind on the receptor. In 2000, the first GPCR crystal structure was elucidated by Palczewski and colleagues.¹³⁴ By 2007, Rasmussen et al. reported the first crystal structure of a GPCR with a diffusible ligand, expanding the knowledge of GPCR subfamilies and turning the focus of the field to drug discovery and pharmacological intervention.¹³⁵ Further efforts in understanding receptor diversity were

¹³⁴ Stenkamp R.E., *et al.* Crystal structure of rhodopsin: A G protein-coupled receptor. 3 *ChemBioChem*. **2002** 963-67, (hereinafter “Stenkamp,” EX1062). Stenkamp published in 2002 in the peer-reviewed periodical *ChemBioChem*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Stenkamp describes the first reported GPCR crystal structure. *See generally* EX1062.

¹³⁵ Rasmussen SG, Choi HJ, Rosenbaum DM, Kobilka TS, Thian FS, Edwards PC, Burghammer M, Ratnala VR, Sanishvili R, Fischetti RF, Schertler GF, Weis WI, Kobilka BK. Crystal structure of the human beta2 adrenergic G-protein-coupled receptor. *Nature*. **2007** Nov 15;450(7168):383-7, (hereinafter “Rasmussen,” EX1063). Rasmussen published in 2007 in the peer-reviewed periodical *Nature*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent.

widespread; the GPCR Network out of Scripps and the Protein Data Bank at Brookhaven National Laboratories both contributed to GPCR structure-function elucidation, amassing more than 20 GPCR structures across subclasses by the end of 2014.^{136,137}

86. While the full structure of GIPR and GLP1R had not been experimentally resolved by 2015, the crystal structure of the glucagon receptor (GCGR) was defined in 2013 by Siu et al.¹³⁸ When discussing the implications of the GCGR structure on peptide ligand binding and pharmacological developments in type 2 diabetes, Siu et al. described an observed overlap between Class B GPCR binding sites, “[suggesting] that, despite possible structural differences between

Rasmussen was the first reported crystal structure of a GPCR with a diffusible ligand. *See generally* EX1063.

¹³⁶ Stevens, R. C., Cherezov, V., Katritch, V., Abagyan, R., Kuhn, P., Rosen, H., & Wüthrich, K. The GPCR Network: a large-scale collaboration to determine human GPCR structure and function. *Nat Rev Drug Discovery*, **2013**;12(1), 25–34, (hereinafter “Stevens,” EX1064). Stevens published in 2013 in the peer-reviewed periodical *Nature Reviews Drug Discovery*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1064, 31-33.

¹³⁷ Berman, H. M., Westbrook, J., Feng, Z., Gilliland, G., Bhat, T. N., Weissig, H., Shindyalov, I. N., & Bourne, P. E. The Protein Data Bank. *Nuc Acids Res*, **2000**; 28(1), 235–242, (hereinafter “Berman,” EX1065). Berman published in 2000 in the peer-reviewed periodical *Nucleic Acids Research*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1065, 238.

¹³⁸ EX1037 (Siu), Abstract, 444.

class B GPCRs, the GCGR crystal structure might offer new opportunities to construct structural models to describe interactions between peptide ligands and other class B GPCRs. This is particularly exciting for those receptors involved in glucose regulation, including GLP1R and GIPR.”¹³⁹ Siu’s observations were consistent with the literature discussed above addressing the common mechanism of the core domain of Class B GPCRs. Accordingly, practitioners used GCGR core domain structure to make inferences about the structure of the core domain of GLP-1R and GIPR.

87. By 2015, the structure of endogenous GLP-1 in a dodecylphosphocholine micelle was known. While residues 1-6 of the pro-peptide were unstructured when analyzed, N-terminal residues 7-14 and 18-29 formed two helices separated by a linker region formed around Gly with the helical structure more pronounced at the C-terminus.¹⁴⁰ The structure of the GLP-1R NTD also was described, including its interaction with the signaling ligand at separate hydrophobic and hydrophilic faces of the ligand.¹⁴¹ Accordingly, the literature

¹³⁹ *Id.*, 448.

¹⁴⁰ EX1030 (Donnelly), 30.

¹⁴¹ EX1030 (Donnelly), 33-34 (NTD/GLP-1 interaction: ligand residues Ala¹⁸, Lys²⁰, and Gly²⁹ interact with Glu residues on receptor NTD domain; principal ligand contacts with NTD are hydrophobic interface formed by residues Ala¹⁸, Ala¹⁹, Phe²², Ile²³, Leu²⁶, and Val²⁷); *see also* Figure 3.

provided significant predictability as to residues (especially C-terminal residues) that would be employed without sacrificing affinity or selectivity for the receptor.

88. For example, it was known that avoiding an MNT motif at positions 27-30 of the C-terminus of the peptide was important to maintain selectivity against the glucagon NTD:

[R]eplacement of the C-terminal sequence 'VKGR' of GLP-1 with the corresponding 'MNT' of glucagon resulted in a 475-fold decrease in affinity. However, the substitution of residues in the N-terminal half of GLP-1 for those of glucagon had much smaller effects...[S]electivity of GLP-1R for GLP1 over glucagon is due to the NTD recognizing the C-terminus of the peptide, while the toleration of GLP-[1]R for the glucagon N-terminal sequence results from the core domain.¹⁴²

89. In contrast, the N-terminal region was directed to interacting with the core domain (i.e., signaling).¹⁴³ C-terminal-truncated analogues thus achieved full GLP-1R potency with minor substitutions.¹⁴⁴ Indeed, an N-terminal GLP-1 fragment 11-mer with a Tyr substitution at His¹ demonstrated potency that was

¹⁴² EX1030 (Donnelly), 30.

¹⁴³ EX1030 (Donnelly), 27-30.

¹⁴⁴ EX1030 (Donnelly), 30 ("Understanding the specificity requirements for GLP-1 and glucagon at GLP-1R and the glucagon receptor has enabled the design of co-agonist peptide that eliminates obesity in a rodent model.... Full potency was obtained at GLP-1R using a peptide corresponding to glucagon, but with changes at just three side chains ([Ser10-Glu, Arg12-Ala, Gln14-Lys] and amidation of the C-terminus.").

only marginally lower than endogenous GLP-1.^{145,146} Additionally, Phe²² and Ile²³ were identified as important positions for maintaining the helical structure.^{147,148}

90. Moreover, the literature identified receptor core domain amino acid residues important in forming the binding site of the peptide's N-terminus and likely to be important for the agonist-induced activation of the receptor.¹⁴⁹ The literature predicted that the core domain formed a deep binding pocket for the His¹ of GLP-1, that Thr⁵ was close to Tyr¹⁴⁵ and Tyr²⁰⁵ on the receptor, and that Lys²⁶ and Leu²⁰ of GLP-1 were placed close to Glu¹³³ and Tyr²⁹⁷ of the receptor core domain.¹⁵⁰

¹⁴⁵ EX1030 (Donnelly), 29 (GLP-1 control EC₅₀ 2.6 ± 0.4 nM, Ala substitution >10⁴ nM).

¹⁴⁶ Xiao Q, Giguere J, Parisien M, Jeng W, St-Pierre SA, Brubaker PL, Wheeler MB. Biological activities of glucagon-like peptide-1 analogues in vitro and in vivo. *Biochemistry*. **2001** Mar 6;40(9):2860-9, (hereinafter "Xiao," EX1066). Xiao published in 2001 in the peer-reviewed periodical *Biochemistry*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1066, 2863, Table 2 (GLP-1 control EC₅₀ 2.6 ± 0.5 nM, Tyr substitution 33.7 ± 2.7 nM).

¹⁴⁷ EX1030 (Donnelly), 29.

¹⁴⁸ EX1067 (Adelhorst), 6277. Adelhorst described alanine substitutions at C-residues of GLP-1 did not drastically affect potency or affinity, with the exception of alanine substitutions at Phe²⁸ and Ile²⁹.

¹⁴⁹ EX1030 (Donnelly), 35. Table 1 (W297-T298, R299-N300, Y305-W306, L307-I308, I309-R310).

¹⁵⁰ EX1030 (Donnelly), 35.

91. Maintaining activity at the N-terminus was the focus when making GLP-1 agonists.¹⁵¹ By 1995, Adelhorst and colleagues had thoroughly annotated the SAR of GLP-1 peptide and the GLP-1 receptor through their systematic replacement of each GLP-1 residue.¹⁵² In so doing, they identified several key amino acids that contribute to receptor interaction. Adelhorst reported that residues His¹, Gly⁴, Phe⁶, Thr⁷, Asp⁹, Phe²², and Ile²³, shown in orange (Figure 3) in alignment for the activated peptide, are involved in GLP-1 receptor binding.¹⁵³ In addition, Adelhorst reported that His¹, Gly⁴, Asp⁹, and Phe²², shown in green (Figure 3), are involved in receptor activation and cited that the N-terminal region of the peptide as important for receptor binding, while the C-terminal region was more important for receptor recognition.¹⁵⁴ Manandhar and Ahn also interpreted Adelhorst's findings in 2014, concluding "On the basis of these results, it is hypothesized that the N-terminal region of GLP-1 is more critical for activating the receptor, whereas the C-terminal region mainly contributes to receptor binding."¹⁵⁵

¹⁵¹ EX1030 (Donnelly), 35.

¹⁵² EX1067 (Adelhorst), 6277.

¹⁵³ *Id.*, 6276-77.

¹⁵⁴ *Id.*, 6277.

¹⁵⁵ Manandhar B, Ahn JM. Glucagon-like peptide-1 (GLP-1) analogs: recent advances, new possibilities, and therapeutic implications. *J Med Chem.* **2015** Feb 12;58(3):1020-37, (hereinafter "Manandhar," EX1068). Manandhar was published in 2015 in the peer-reviewed periodical *Journal of Medicinal Chemistry*, is a reference within the same field at issue that is reasonably pertinent to the issues

In contrast, others residues (e.g., endogenous peptide positions 24, 27, and 30) were suggested to be non-critical for affinity or activity.¹⁵⁶

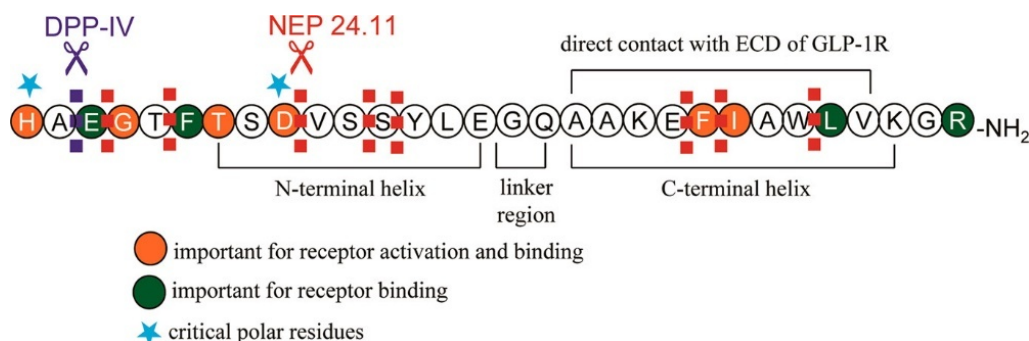


Figure 3.

92. By 2015, both GLP-1 and GIP agonist peptides were being synthesized for applications *in vitro* and *in vivo*.^{157,158} Notably, a dual incretin GLP-1/GIP agonist exhibited “enhanced antihyperglycemic and insulinotropic efficacy relative to selective GLP-1 agonists.”¹⁵⁹ Figures 4 and 5 below demonstrate great progress had already been made in GIP/GLP-1 dual agonist research. At this point in time, Finan et al. had established core sequences that would lead to GLP-1/GIP co-agonism without glucagon agonism. For example,

addressed, and should therefore be considered as prior art to the challenged patent. EX1068, 1021.

¹⁵⁶ EX1030 (Donnelly), 29 (“The non-involvement of these residues in receptor affinity and efficacy is reflected in the results of the Ala scan”).

¹⁵⁷ EX1059 (Day), Table 1, 751.

¹⁵⁸ EX1061 (Finan), 2.

¹⁵⁹ *Id.*, Abstract.

removing the MNT at positions 27 to 29 of a co-agonist peptide significantly reduced glucagon agonism. (Figure 4,5).¹⁶⁰

No.	Analog	GLP-1R			GIPR			GCGR		
		EC ₅₀ (nM)	SD	Relative GLP-1 %	EC ₅₀ (nM)	SD	Relative GIP %	EC ₅₀ (nM)	SD	Relative glucagon %
1	GLP-1	0.028	0.002	100	1513.825	78.950	0	2449.288	106.460	0
2	Exendin-4	0.004	0.001	621	2.952	0.841	1	186.147	16.677	0
3	GLP-1 (Aib ² E ¹⁶ Cex K ⁴⁰)	0.017	0.003	158	1200.336	100.003	0	2000.659	500.000	0
4	Liraglutide	0.011	0.003	249	78.657	7.620	0	172.929	22.561	0
5	GIP	1567.012	65.780	0	0.020	0.004	100	417.480	10.370	0
6	GIP (Aib ²)	3527.099	310.810	0	0.016	0.001	126	1459.502	123.800	0
7	GIP (Aib ² Cex K ⁴⁰ -C ₁₆ acyl)	6.330	2.690	0	0.012	0.001	168	2.920	0.840	1
8	Glucagon	3.100	0.494	1	1538.109	329.020	0	0.032	0.006	100
9	Glucagon (Aib ² K ¹⁰ -γEγE-C ₁₆ acyl Aib ²⁰)	0.479	0.068	6	22.650	6.100	0	0.005	0.001	616
10	Glucagon (E ¹⁶ Q ¹⁷ A ¹⁸ K ²⁰ E ²¹ I ²³ A ²⁴)-NH ₂	0.022	0.002	126	6.258	1.278	0	0.030	0.009	104
11	Peptide 10 (I ¹⁷ H ¹⁸ Q ¹⁹)-NH ₂	0.140	0.019	20	5.530	1.099	0	0.150	0.022	21
12	Peptide 11 (Q ¹⁷ A ¹⁸ A ¹⁹ Cex)-NH ₂	0.020	0.002	138	14.557	2.241	0	0.060	0.003	53
13	Peptide 12 (Y ¹)-NH ₂	0.120	0.008	23	3.054	0.663	1	0.060	0.003	53
14	Peptide 13 (V ²³ N ²⁴ L ²⁷ A ²⁸)-NH ₂	0.040	0.001	69	0.557	0.069	4	0.040	0.002	79
15	Peptide 14 (Aib ² I ¹²)-NH ₂	0.010	0.001	276	0.176	0.019	11	0.190	0.039	17
16	Peptide 15 (Aib ²⁰ (-)lactam C ⁴⁰)-NH ₂	0.024	0.009	115	0.040	0.007	50	3.457	0.699	1
17	Peptide 16 (E ³ K ¹⁶)-NH ₂	0.012	0.002	230	0.003	0.001	673	58.947	8.284	0
18	Peptide 17 (K ⁴⁰)-NH ₂	0.016	0.002	177	0.010	0.002	202	6.908	1.586	0
19	Peptide 18 (K ⁴⁰ -C ₁₆ acyl)-NH ₂	0.005	0.001	509	0.003	0.001	691	1.286	0.103	2
20	Peptide 18 (C ²⁴)-NH ₂	0.024	0.004	117	0.006	0.001	337	12.192	1.433	0
21	Peptide 20 (C ²⁴ -40 kD PEG)-NH ₂	0.323	0.028	9	0.194	0.043	10	358.500	44.770	0

Figure 4.¹⁶¹

¹⁶⁰ *Id.*

¹⁶¹ *Id.*, Supplemental.

Glucagon	HSQGTFTSDYSKYLDSRRRAQDFVQWLMNT-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	HXQGTFTISDK ^c SKYLDXRAAQDFVQWLMDT-OH
Peptide 10	HSQGTFTSDYSKYLD <u>EQAAKEFIAWLMNT</u> -NH ₂
Peptide 11	HSQGTFTSDYSKYLD <u>EIHQKEFIAWLMNT</u> -NH ₂
Peptide 12	HSQGTFTSDYSKYLD <u>EQAAKEFIAWLMNGGPSSGAPPPS</u> -NH ₂
Peptide 13	YSQGTFTSDYSKYLD <u>EQAAKEFIAWLMNGGPSSGAPPPS</u> -NH ₂
Peptide 14	YSQGTFTSDYSKYLD <u>EQAAKEFVNWLLAGGPSSGAPPPS</u> -NH ₂
Peptide 15	YXQGTFTSDYSIYLD <u>EQAAKEFVNWLLAGGPSSGAPPPS</u> -NH ₂
Peptide 16	YXQGTFTSDYSIYLD <u>EQAAKEFVNWLLAGGPSSGAPPPSC</u> -NH ₂
Peptide 17	YXEGTFTSDYSIYLD <u>KQAAXEFVNWLLAGGPSSGAPPPSC</u> -NH ₂
Peptide 18	YXEGTFTSDYSIYLD <u>KQAAXEFVNWLLAGGPSSGAPPPSK</u> -NH ₂
Peptide 19	YXEGTFTSDYSIYLD <u>KQAAXEFVNWLLAGGPSSGAPPPSK^b</u> -NH ₂
Peptide 20	YXEGTFTSDYSIYLD <u>KQAAXEFVCWLLAGGPSSGAPPPSK</u> -NH ₂
Peptide 21	YXEGTFTSDYSIYLD <u>KQAAXEFVC[*]WLLAGGPSSGAPPPSK</u> -NH ₂

X=aminoisobutyric acid =lactam
 K^a=Lys-γE-C₁₆ acyl K^b=Lys-C₁₆ acyl K^c=Lys-γEγE-C₁₆ acyl C^{*}=Cys-40kDa PEG

Figure 5.¹⁶²

93. With these successes, skilled artisans were provided further motivation to make GIP/GLP-1 receptor dual agonist peptides to improve duration of action and avoid unnecessary immunogenicity.

94. A prominent approach applied individually to GLP-1 and GIP receptor agonists, as well as to GIP/GLP-1 receptor dual agonists, was to apply the known C-terminal motif (GGPSSGAPPPS) found naturally in the endogenous

¹⁶² *Id.*

GLP-1 receptor agonist exendin and employed successfully in the synthetic GLP-1 agonist exenatide. Discovery of the natural GLP-1 receptor agonists derived from Gila monster saliva led to rapid exploration of the SAR explaining both the superior potency¹⁶³ and proteolytic stability¹⁶⁴ of the exendin-3 and -4 (sequences shown below) peptides as compared to GLP-1 and GIP.

Exendin-3

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
H	S	D	G	T	F	T	S	D	L	S	K	Q	M	E	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S

Exendin-4

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S

Exendin-3 and -4 differ from one another only by the residues employed at positions 2 and 3 (annotated with red font herein).¹⁶⁵ An additional, recognized advantage of this C-terminal motif was its favorable profile avoiding anti-drug antibodies in exenatide and liraglutide, which antibodies were known to reduce safety and

¹⁶³ 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.”).

¹⁶⁴ 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.

¹⁶⁵ *Id.*, 6, Table 1.

efficacy of peptide based drugs.^{166,167} Because of these favorable properties, it was common and routine to append the C-terminal exendin motif to extend GLP-1 analogues or to replace the C-terminal residues of GIP analogues.

95. One important source of metabolic stability was the exendins' inhibition of DPP-IV-catalyzed cleavage of the N-terminus of the peptides at the penultimate Ala² residue, which essentially deactivates the peptides' incretin activity.¹⁶⁸ The exendins effectively inhibit this metabolic deactivation by employing either a Ser residue or a Gly residue in place of the Ala residue at position 2.

¹⁶⁶ Fineman MS, *et al.*, Clinical relevance of anti-exenatide antibodies: safety, efficacy and cross-reactivity with long-term treatment. *Diabetes Obes Metab.* 2012 Jun;14(6):546-54, (hereinafter "Fineman" EX1070). Fineman was published in 2012 in the peer-reviewed periodical *Diabetes, Obesity, and Metabolism*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1070, Abstract.

¹⁶⁷ Buse J. B., *et al.*, Liraglutide Treatment Is Associated with a Low Frequency and Magnitude of Antibody Formation with No Apparent Impact on Glycemic Response or Increased Frequency of Adverse Events: Results from the Liraglutide Effect and Action in Diabetes (LEAD) Trials, *The Journal of Clinical Endocrinology & Metabolism*, Volume 96, Issue 6, 1 June 2011, Pages 1695–1702, (hereinafter "Buse," EX1071). Buse was published in 2011 in the peer-reviewed periodical *The Journal of Clinical Endocrinology & Metabolism*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1071, 1700-1701, Abstract.

¹⁶⁸ EX1069 (Thum), 4-6.

96. But the proteolytic stability of the exendins goes far beyond the substitution at residue 2.¹⁶⁹ Instead, the superior metabolic stability and GLP-1 receptor agonist activity of exendins was traced specifically to the C-terminal motif, which forms a Trp-cage fold.¹⁷⁰ 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 neutral endopeptidases.¹⁷¹ The C-terminal motif was understood to compensate for the disruption to the binding affinity caused by the replacement of the Ala² at the N-terminus.¹⁷² In contrast, truncating the peptides to fewer than 28 amino acids significantly negated their incretin effects.¹⁷³ The formation of the

¹⁶⁹ EX1069 (Thum), 8 (“The exendins possess DPP-IV-resistant primary structures, but this does not explain their remarkable resistance to proteolysis. They are each several orders of magnitude more stable than GLP-1 and the DPP-IV resistant SER-8-GLP-1. This suggests that conformational aspects of the molecular structure of the exendins may be important for imparting metabolic stability and may be the basis for the development of novel metabolically-stable analogs.”).

¹⁷⁰ Doyle M.E., *et al.* The importance of the nine-amino acid C-terminal sequence of exendin-4 for binding to the GLP-1 receptor and for biological activity. *Regul Pept.* **2003** Jul 15;114(2-3):153-8, (hereinafter “Doyle,” EX1072). Doyle published in 2003 in the peer-reviewed periodical *Regulatory Peptides*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1072, Abstract, 157.

¹⁷¹ *Id.*, Abstract, 155-157.

¹⁷² *Id.*, 157.

¹⁷³ *Id.*, Abstract, 155-157.

Trp-cage fold by the C-terminal motif additionally was understood to provide metabolic stability to the peptides, especially by reducing the rate at which the peptides were cleared by the kidneys and peripheral tissues.¹⁷⁴ 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-1.¹⁷⁵ 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.¹⁷⁶

97. Researchers subsequently demonstrated that the C-terminal motif similarly improved proteolytic resistance and insulintropic activity of GIP without

¹⁷⁴ Simonsen L., Holst J.J., Madsen, K., Deacon C.F The C-terminal extension of exendin-4 provides additional metabolic stability when added to GLP-1, while there is minimal effect of truncating exendin-4 in anaesthetized pigs. *Regulatory Peptides*. **2013** Feb 10;181:17-21, (hereinafter “Simonsen,” EX1073). Simonsen published in **2013** in the peer-reviewed periodical *Regulatory Peptides*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1073, Abstract.

¹⁷⁵ *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.”).

¹⁷⁶ *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.”).

adversely affecting binding potency or functional activity at the GIP receptor relative to native GIP or DPP-IV-resistant GIP.¹⁷⁷ Researchers proposed that the random, flexible coil provided by the endogenous GIP C-terminal motif was responsible for undesirable lipogenic activity of GIP, and thus proposed replacing it with the exendin C-terminal motif to avoid undesirable lipogenesis.¹⁷⁸

98. Co-administration of the analogue of GIP with the C-terminal exendin motif together with an exenatide analogue GLP-1 agonist (comprising the C-terminal exendin motif) demonstrated greater glucose-lowering effects *in vivo* than either monotherapy alone without causing undesirable lipogenesis.¹⁷⁹ Researchers thus proposed therapeutic treatment of type-2 diabetes through dual GIP/GLP-1

¹⁷⁷ Tatarkiewicz, K., et al., A novel long-acting glucose-dependent insulinotropic peptide analogue: enhanced efficacy in normal and diabetic rodents. *Diabetes, obesity & metabolism*, **2014** (1), 75–85, (hereinafter “Tatarkiewicz,” EX1074). Tatarkiewicz published in 2014 in the peer-reviewed periodical *Diabetes*, is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. EX1074, Abstract, 75-79, 82-84 & Table 1 (discussing C-terminally extended GIP analogue AC163794).

¹⁷⁸ *Id.*, 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.”).

¹⁷⁹ *Id.*, Abstract, 84 (glucose-lowering effect in combination with AC3174 was markedly improved).

agonism employing the exendin C-terminal motif.¹⁸⁰ Though the exenatide C-terminal motif materially improved the duration of action of GIP/GLP-1 agonists, POSAs routinely further increased the duration of action of exenatide-motif-comprising GIP/GLP-1 agonists to achieve half-lives similar or longer than that of semaglutide.¹⁸¹ This was accomplished by conjugating the peptide to the known albumin-binding moiety ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆₋₁₈-CO₂H). Though the reported half-lives were reported in mice, the literature ultimately reported that the half-life of semaglutide was sufficient to achieve once-weekly dosing.¹⁸²

VIII. THE ASSERTED REFERENCES DISCLOSE OR SUGGEST EACH OF THE CLAIMED FEATURES

99. 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 '780 patent.

¹⁸⁰ *Id.*, Abstract, 84.

¹⁸¹ EX1075 (WO 2015/067,715, the '715 Application). The '715 Application has a priority date of November 6, 2013, was filed on November 6, 2014, and published on May 14, 2015. The '715 Application is a reference within the same field at issue that is reasonably pertinent to the issues addressed, and should therefore be considered as prior art to the challenged patent. Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51 (Table 1), 58 (Table 4).

¹⁸² See Section VIII.C below.

A. WO 2011/119657 A1

100. International Publication No. WO 2011/119657, entitled “NOVEL PEPTIDES AND METHOD FOR THEIR PREPARATION AND USE” (the ‘657 Publication) published on September 29, 2011, based on applications filed by Eli Lilly & Co. on March 23, 2011 and March 26, 2010. Accordingly, I have been advised that the ‘657 Publication is prior art to the ‘780 patent.

101. The ‘657 Publication 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 GCGR.¹⁸³ The ‘657 Publication discloses that GIP and GLP-1 are known incretins, that incretin receptor signaling exerts physiologically relevant action critical for glucose homeostasis, and that the efficacy of GIP for lowering glucose in type 2 diabetic patients is increased and becomes close to that observed in a normoglycemic subject after some glucose-lowering is already achieved.¹⁸⁴ The ‘657 Publication discloses that GLP-1 is effective at lowering glucose in both healthy and diabetic subjects, but that using it at full efficacy causes nausea.¹⁸⁵ Accordingly, the ‘657 Publication provides “new potent and efficacious peptides with amino acid substitution introduced to

¹⁸³ EX1007, Abstract.

¹⁸⁴ EX1007, 1:8-21.

¹⁸⁵ EX1007, 1:21-23.

modulate activity for both GIP and GLP-1 while maintaining selectivity over glucagon” to use the glucose-lowering effects of GLP-1 to better harness the insulin-secretion effects of GIP.¹⁸⁶ The ’657 Publication teaches that administration of these peptides is useful for reducing body weight, in addition to increasing glucose sensitivity.¹⁸⁷

102. 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: 1.¹⁸⁸ As set forth by the ’657 Publication, 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 Ala²⁸.¹⁸⁹ SEQ

ID NO: 1 also comprises a C-terminal tail having the following sequence: Aib K G K 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.¹⁹⁰ The ’657 Publication teaches that the

¹⁸⁶ EX1007, 2:5-8.

¹⁸⁷ EX1007, 2:9-10.

¹⁸⁸ EX1007, Abstract, 2:12-20 (“The present invention provides a peptide comprising the sequence...(SEQ ID NO: 1)”), Claims 1-12.

¹⁸⁹ EX1007, 2:12-25, 5:24-27.

¹⁹⁰ EX1007, 2:12-25.

peptides are stable against rapid metabolic deactivation by DPP-IV.¹⁹¹ The '657 Publication teaches routine methods for making the peptides.¹⁹²

103. The '657 Publication 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.¹⁹³

104. The '657 Publication reports results of a GIPR binding assay that it says demonstrate that all peptides of Table 1 bind to GIPR and may activate that receptor, in turn triggering GIP-dependent physiological responses.¹⁹⁴ The K_i values ranged from 0.023 nM to 9.79 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).¹⁹⁵

105. The '657 Publication reports results of a GLP-1-R binding assay that it says demonstrate that all peptides of Table 2 bind to GLP-1-R and may activate

¹⁹¹ EX1007, 5:22-23.

¹⁹² EX1007, 7:7-8:5.

¹⁹³ EX1007, 11:20-27.

¹⁹⁴ EX1007, 11:29-13:10.

¹⁹⁵ EX1007, 13:7-8 & Table 1.

that receptor, in turn triggering GLP-1-dependent physiological responses.¹⁹⁶ 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).¹⁹⁷ 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).

106. The '657 Publication reports results of a glucagon-R binding assay that it says demonstrates that no peptides of Table 3 initiate GLGR-mediated physiological responses.¹⁹⁸ 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).¹⁹⁹

107. The '657 Publication reports results of an assay evaluating functional activation of hGIPR cells or hGLP-1R cells to generate intracellular cAMP that it says demonstrate that all of Example peptides 1-5 bind and activate both GIPR and

¹⁹⁶ EX1007, 13:12-15:3 & Table 2.

¹⁹⁷ EX1007, 15:1-3 & Table 2.

¹⁹⁸ EX1007, 15:4-16:25 & Table 3.

¹⁹⁹ EX1007, 16:22-23 & Table 3.

GLP-1R and can thereby initiate GIPR and GLP-1R-mediated physiological responses.²⁰⁰ 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 analogue (0.005-0.023 nM). 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 analogues achieved comparable efficacy in cell assays, while PEGylation reduced potency somewhat.

108. The '657 Publication reports *in vivo* experiments in which administration of any one 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.²⁰¹ The '657 Publication also reports *in vivo* experiments in which administration of any one of Example peptides 3-5 to obese mice or normal rats resulted in dose-dependent decreases in blood glucose as compared to vehicle.²⁰² The '657 Publication also reports that administration of

²⁰⁰ EX1007, 17:1-19:7 & Tables 4-5.

²⁰¹ EX1007, 19:8-20:9, 21:9-22:15 & Tables 6a-6b.

²⁰² EX1007, 20:10-21:8, 23:1-24:2 & Tables 7a-7b.

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.²⁰³

109. The '657 Publication teaches treating diabetes and/or obesity by administering to a patient in need thereof an effective amount of a peptide of the invention.²⁰⁴ The '657 Publication teaches formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient, including together with other therapeutic agents.²⁰⁵ 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.²⁰⁶ 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.”²⁰⁷

B. WO 2013/164483 A1

110. International Publication No. WO 2013/164483, entitled “GIP-GLP-1 DUAL AGONIST COMPOUNDS AND METHODS” (the '483 Publication)

²⁰³ EX1007, 22:15-30.

²⁰⁴ EX1007, 3:32-4:14 (“method for inducing weight loss”), Claims 15-19.

²⁰⁵ EX1007, 4:26-5:21, Claims 13-14.

²⁰⁶ EX1007, 25:4-9.

²⁰⁷ EX1007, 25:9-20.

published on November 7, 2013, based on applications filed by Zealand Pharma A/S on May 3, 2013, February 15, 2013, and May 3, 2012. Accordingly, I have been advised that the '483 Publication is prior art to the '780 patent.

111. The '483 Publication relates to truncated GIP analogues altered as compared to wild-type GIP to have increased GLP-1 activity, making them GIP/GLP-1 dual agonist compounds.²⁰⁸ The '483 Publication discloses that GIP and GLP-1 are known incretins.²⁰⁹ GLP-1 and a related peptide hormone glucagon arise from the same precursor peptide, pre-proglucagon. GIP arises from a different precursor, pre-pro-GIP. The '483 Publication teaches that diabetes already was being treated using injectable GLP-1 receptor agonists ByettaTM (twice-daily exenatide injection)²¹⁰, BydureonTM (once weekly exenatide injection)²¹¹, VictozaTM (once-daily liraglutide injection)²¹², and SaxendaTM (once-daily liraglutide injection)²¹³ and using oral DPP-IV inhibitors designed to reduce the enzymatic inactivation of endogenous GLP-1 and GIP.²¹⁴

²⁰⁸ EX1008, Abstract.

²⁰⁹ EX1008, [0002].

²¹⁰ EX1054 (BYETTA), 1-2.

²¹¹ EX1053 (BYDUREON), 1, 16.

²¹² EX1050 (VICTOZA), 1, 11.

²¹³ EX1013 (SAXENDA), 1, 14.

²¹⁴ EX1008, [0003].

112. The '483 Publication describes a rationale for employing GLP-1 agonism together with GIP agonism to treat diabetes and/or obesity. For example, the '483 Publication explains that both GLP-1 and GIP agonists were known to protect pancreatic beta-cells by inhibiting apoptosis and enhancing proliferation.²¹⁵ It explains that the combination therapy of GLP-1 receptor agonist liraglutide and GIP “showed superior glucose-lowering and insulintropic effect compared to treatment with Liraglutide and GIP alone.”²¹⁶ In addition to improving blood glucose control, the '483 Publication teaches that GIP may also enhance GLP-1-mediated body weight loss.²¹⁷ Though chronic treatment with GLP-1 receptor agonists cause significant weight loss in diabetic patients, the '483 Publication teaches that body weight loss associated with GLP-1 agonist treatment is enhanced when GLP-1 and GIP are co-administered.²¹⁸ Accordingly, the '483 Publication teaches substitutions to truncated GIP analogues that increase their GLP-1 activity to create dual GIP/GLP-1 agonists that are “superior to existing and marketed GLP-1 analogues” by offering “improved glycemic control and enhanced body weight loss,” such that they may be “used as therapeutics for type 2 diabetes

²¹⁵ EX1008, [0003].

²¹⁶ EX1008, [0003].

²¹⁷ EX1008, [0004].

²¹⁸ EX1008, [0004].

mellitus, obesity, and related disorders.”²¹⁹

113. The '483 Publication describes successfully creating and testing dozens of GLP-1/GIP dual agonist peptides.²²⁰ It describes measuring both GIP and GLP-1 receptor activity of the synthesized peptides *in vitro* and *in vivo*.²²¹ Many of the EC₅₀ values reported approach those reported for endogenous ligand, including for peptides conjugated to lipophilic substituents.²²² The ratio of GIP potency to GLP-1 potency often is balanced within a range of 1:2-2:1.

114. The *in vivo* results showed that even compounds without the most potent EC₅₀ results *in vitro* achieved superior results in lowering glucose and body weight compared to liraglutide *in vivo*, even using much lower doses.²²³ For example, Compound 33 achieved comparable body weight reductions to liraglutide using one-fifth of the dose, and achieved greater weight reduction with additional dosing.²²⁴ With murine terminal half-lives in the low single digit hours,²²⁵ a POSA

²¹⁹ EX1008, [0005].

²²⁰ EX1008, [0109]-[0114] (Compound 1-59 sequences and synthesis methods).

²²¹ EX1008, [0115] (Table 3: *in vitro*), [0117] (*in vivo*).

²²² EX1008, Table 3 (GLP-1: 0.0051-2.6 nM; GIP: 0.0068, 0.012 vs. 0.0038 nM).

²²³ EX1008, [0117]-[0119] & Figs. 1-7.

²²⁴ EX1008, Fig. 2.

²²⁵ EX1008, [0116] & Table 4.

had good reason to modify truncated or C-terminal-motif-substituted GIP/GLP-1 receptor dual agonists to further decrease the required frequency of dosing.

115. To analyze the SAR provided by the '483 Publication, Tables A and B below present the most potent GIP/GLP-1 agonists sorted respectively based on the lowest (most potent) GIP or GLP-1 EC₅₀ values. Gathering together data from two related tables from the '483 Publication (EX1008, [0109], [0115], Tables 1, 3), Tables A and B display EC₅₀ data for the compounds together with the amino acid sequences of the respective compounds. Residues highlighted in green (2-6, 8-9, 11, 22, and 25-26) are identical to the amino acid sequence shared by GLP-1 and GIP, consistent with prior art teachings. Residues in dark blue follow the endogenous GLP-1 sequence and residues in light blue follow the endogenous GIP sequence.

Table A

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	GIP	GLP-1	
GIP	Y	A	E	G	T	F	T	S	D	Y	S	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K														
GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R	G	NH2													
Liraglutide	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K**	E	F	I	A	W	L	V	R	G	R	G														
Exenatide	H	A	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2						
Compound 2	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Alb	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2			0.0068	0.015	
Compound 55	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	H	D	F	V	E	W	L	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2			0.0071	0.0087	
Compound 39	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	K	E	F	V	E	W	L	L	S	A	NH2													0.0083	0.011	
Compound 43	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	E	W	L	L	S	A	NH2													0.0091	0.017	
Compound 37	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2													0.0097	0.018	
Compound 36	Y	Alb	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K**	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2			0.0099	0.015	
Compound 40	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2													0.011	0.022	
Compound 32	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Alb	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2			0.012	0.018	
Compound 41	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2													0.013	0.011	
Compound 3	Y	Alb	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	NH2													0.015	0.022
Compound 19	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	K	E	F	V	N	W	L	L	A	Alb	K	NH2													0.015	0.0073
Compound 44	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	NH2													0.016	0.013	
Compound 17	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.021	0.0074
Compound 31	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K*	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.022	0.020
Compound 29	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	G	P	S	S	G	A	P	P	P	S	NH2			0.024	0.0088	
Compound 35	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2			0.028	0.022	
Compound 5	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.031	0.023
Compound 33	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2			0.035	0.031	
Compound 14	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.036	0.0087
Compound 54	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	K**	A	A	K	E	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2			0.037	0.033
Compound 34	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	E	F	I	E	W	L	E	S	A	NH2													0.045	0.031	
Compound 20	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	K	W	L	L	A	Alb	K	NH2													0.049	0.0090

Table B

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40		42		GIP	GLP-1
GIP	Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q			
GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	**	E	F	I	A	W	L	V	K	G	R	G	NH2												
Liraglutide	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	**	E	F	I	A	W	L	V	R	G	R	G	NH2												
Exenatide	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2						
Compound 28	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.020	0.0051
Compound 19	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	K	E	F	V	N	W	L	L	A	Alb	K	NH2													0.015	0.0073
Compound 17	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.021	0.0074
Compound 24	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.096	0.0085
Compound 55	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				0.0071	0.0087
Compound 14	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.036	0.0087
Compound 29	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	G	P	S	S	G	A	P	P	P	S	NH2				0.024	0.0088
Compound 30	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	N	W	L	L	A	Q	K	NH2													0.054	0.0093
Compound 39	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	K	E	F	V	E	W	L	L	S	A	NH2													0.0083	0.011	
Compound 41	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2													0.013	0.011	
Compound 16	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.053	0.012
Compound 23	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	K	A	Alb	K	NH2													0.42	0.012
Compound 42	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2													0.0070	0.012	
Compound 44	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	NH2													0.016	0.013	
Compound 9	Y	Alb	E	G	T	F	T	S	D	L	S	K	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.091	0.014
Compound 2	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				0.0068	0.015
Compound 36	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2				0.0099	0.015
Compound 18	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	K	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.36	0.015
Compound 43	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	E	W	L	L	S	A	NH2													0.0091	0.017	
Compound 37	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2													0.0097	0.018	
Compound 32	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				0.012	0.018
Compound 38	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2													0.0070	0.018	
Compound 40	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2													0.011	0.022	
Compound 3	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	I	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	NH2													0.015	0.022
Compound 35	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2				0.028	0.022
Compound 5	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.031	0.023
Compound 7	Y	G	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.21	0.024
Compound 8	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2													0.10	0.029
Compound 33	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				0.035	0.031
Compound 34	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	E	F	I	E	W	L	E	S	A	NH2													0.045	0.031	
Compound 13	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	S	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K												0.14	0.032	
Compound 54	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	E	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				0.037	0.033
Compound 48	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	D	F	V	E	W	L	E	S	A	NH2													0.061	0.041	
Compound 25	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	Y	G	Nal	L	D	F	NH2					0.12	0.041		
Compound 46	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K**	A	A	K	E	F	V	E	W	L	L	S	A	NH2													0.088	0.048	
Compound 49	Y	Alb	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	K**	A	A	K	D	F	I	E	W	L	E	S	A	NH2													0.092	0.049	

116. Consistent with previously known SAR, the C-terminal region of the peptides (residues 29 and higher) appear to be relatively unimportant for the peptides to successfully signal through the GLP-1 and GIP receptors, while the N-terminal residues are more important to activate GLP-1 and GIP signaling. The '483 Publication teaches that the authors successfully and readily created dual GIP/GLP-1 agonists using a variety of amino acid residues beginning at positions 29-30, including while truncating the peptide with an amidated amino acid (e.g., lysine or alanine) at position 29 or 30, or adding a known C-terminal motif (e.g., GPSSGAPPPS-amide) beginning at position 30.²²⁶

²²⁶ See, e.g., EX1008, [0109]-[0114].

117. The SAR of the '483 Publication teaches that position 29 is a good location to use alanine, lysine, or the glutamine endogenous to GIP, consistent with its express teaching that the glycine endogenous to GLP-1 also works well at that location.²²⁷ In contrast, use of asparagine at this position was known in the literature to result in selectivity for glucagon rather than GLP-1 and GIP.²²⁸

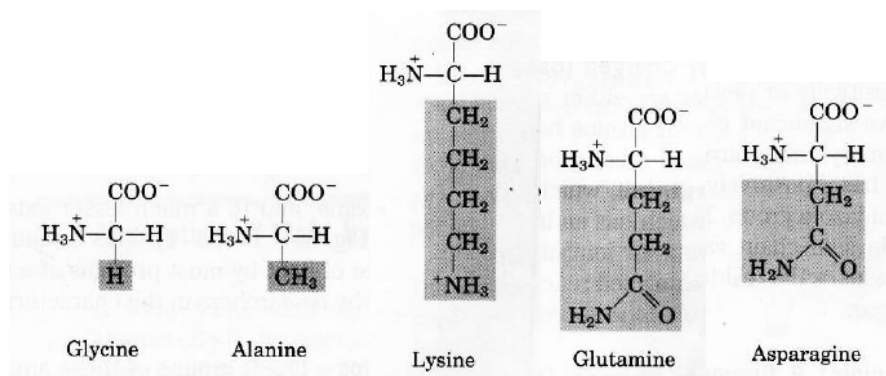


Figure 6.²²⁹

118. The SAR of the '483 Publication teaches that positions 28 is a good location to use the alanine residue that is endogenous to GIP, though the authors readily and successfully made dual agonists using serine or arginine at position 28 as well. In contrast, use of threonine at this position was known in the literature to result in selectivity for glucagon rather than GLP-1 and GIP.²³⁰

²²⁷ See, e.g., EX1008, [0007], [0013], [0017].

²²⁸ See Section VII.C above (VKG vs. MTN).

²²⁹ EX1014, 119, Fig. 5-5.

²³⁰ See Section VII.C above (VKG vs. MTN).

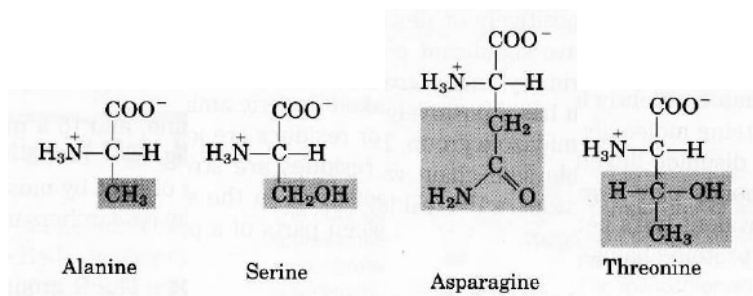


Figure 7.²³¹

119. The SAR of the '483 Publication teaches that position 27 is a good location to use either the leucine endogenous to GIP or the valine endogenous to GLP-1. Together the use of these residues suggests another nonpolar, aliphatic residue that presents a conservative substitution to both of these (i.e., isoleucine), as expressly suggested in the '483 publication.²³² In contrast, use of methionine at this position was known in the literature to result in selectivity for glucagon rather than GLP-1 and GIP.²³³

²³¹ EX1014, 119, Fig. 5-5.

²³² *See, e.g.*, EX1008, [0007].

²³³ *See* Section VII.C above (VKG vs. MTN).

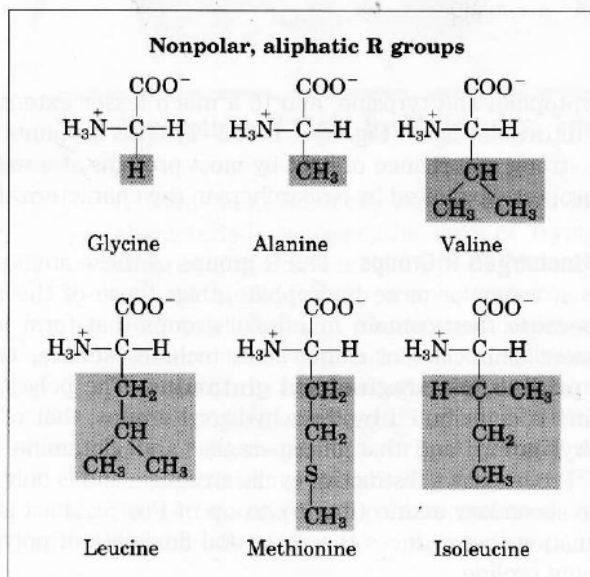


Figure 8.²³⁴

120. The SAR of the '483 Publication teaches that positions 22 and 25-26 are conserved for receptor functionality (though permitting Phe or 1-Nal²³⁵ at 22). For positions 23-24, the '483 publication demonstrates potent dual-agonism using the VN sequence from GIP, while demonstrating that replacing the endogenous asparagine (N) at position 24 with a glutamic acid (E) successfully and readily achieved dual-agonism, including *in vivo*. Based on the structures and charge contrast of asparagine and glutamic acid, a POSA would have understood that glutamine (Gln, Q) was a conservative substitution at position 24 supported by the SAR from the '483 Publication. In fact, the '483 Publication twice identifies it as

²³⁴ EX1014, 119, Fig. 5-5.

²³⁵ EX1008, [0007].

such.²³⁶

I	II	III	IV	V	I	II	III	IV	V
A	N	H	M	F	A	E	H	M	F
S	D	R	L	Y	L	D	R	S	Y
T	E	K	I	W	I		K	T	W
P	Q		V		P			C	
G			C		G			N	
					V			Q	

Figure 9.²³⁷

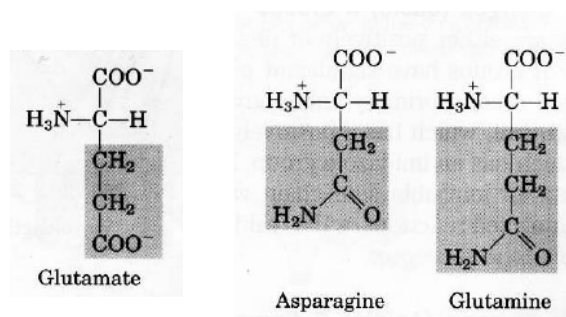


Figure 10.²³⁸

121. The authors readily and successfully created dual agonists using the endogenous aspartic acid or glutamic acid (or using non-endogenous alanine) at

²³⁶ EX1008, [0049]-[0050] (Gln is a conservative substitution for each of N and E, and it additionally preserves the physicochemical properties of the N, (Group II)).

²³⁷ EX1008, [0049]-[0050].

²³⁸ EX1014, 119, Fig. 5-5.

position 21, suggesting the receptors are unlikely to interact specifically with the ligand at that location and are amenable to each of those amino acid residues regardless of charge.

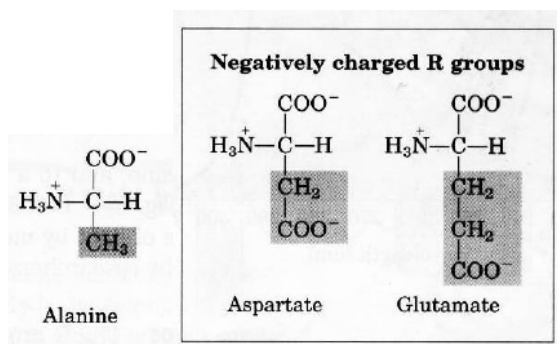


Figure 11.²³⁹

122. The SAR of the '483 Publication teaches position 20 is a prime target for use of the lysine residue endogenous to GLP-1 (particularly if intending to conjugate at 20), though the authors readily and successfully created dual agonists using an arginine or histidine at that location. The SAR thus suggests the receptors are unlikely to interact specifically with the ligand at that location and are amenable to each of those amino acid residues at that location.

²³⁹ EX1014, 119, Fig. 5-5.

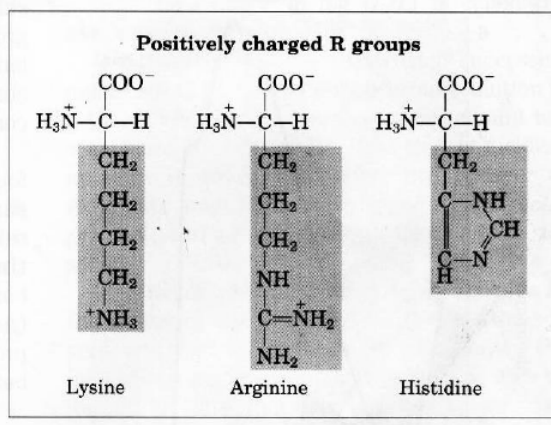


Figure 12.²⁴⁰

123. The SAR of the '483 Publication teaches position 17 is a good position to use a lysine (particularly if intending to conjugate an albumin-binding moiety at 17) or the isoleucine endogenous to GIP, which I have compared below to the more specific glutamine residue endogenous to GLP-1.

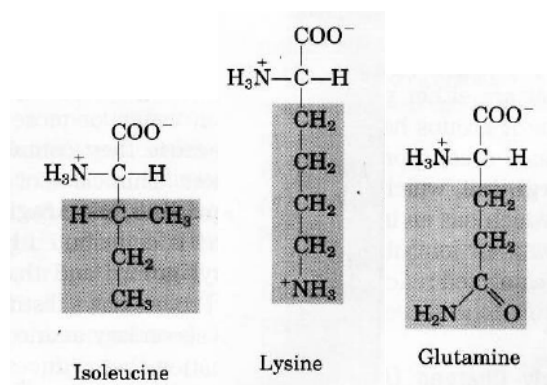


Figure 13.²⁴¹

²⁴⁰ EX1014, 119, Fig. 5-5.

²⁴¹ EX1014, 119, Fig. 5-5.

124. Consistent with the SAR disclosed in the '483 Publication, it teaches that the C-terminal tail of wild-type GIP (positions 30-42) may be deleted entirely or replaced with the familiar exenatide C-terminal motif.²⁴²

125. The '483 Publication teaches placing an Aib in amino acid position 2 may render the GIP peptide resistant to DPP-IV cleavage and that placing one in position 13 and/or 29 “will enhance the stability of the peptide towards enzymatic degradation” and may “enhance the helicity of the peptide and hence enhance the GLP-1 receptor activity,” while “1-Nal in position 22 may also render the peptide stable to enzymatic degradation.”²⁴³

126. It teaches conjugation of the peptides to a lipophilic substituent increases their half-life, including at position 20.²⁴⁴ The '483 Publication explains “it is thought that the lipophilic substituent [conjugated to an amino acid side chain] 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” and “modulate[s] the potency of the compounds, e.g.,

²⁴² EX1008, [0006], [0024] (“it is believed that a truncation of the C-terminal of native GIP may be performed without affecting the GIP receptor activity. The truncation can be of any length (1-13 amino acids) down to the 29 amino acid GIP peptide.”), [0025] (“addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser...at or after position 29 or at or after position 30 of a native GIP or a GIP analogue may increase GLP1 receptor activity.”).

²⁴³ EX1008, [0027].

²⁴⁴ EX1008, [0006].

with respect to the GIP receptor and/or the GLP-1 receptor.”²⁴⁵ The ’483 Publication teaches embodiments in which “only one amino acid side chain is conjugated to a lipophilic substituent, including by conjugating the lipophilic substituent to the amino acid side chain “by one or more spaces Z^2 .”²⁴⁶ The spacer itself may be as long as C1-10 hydrocarbons, or as short as a C1-5 hydrocarbon chain, and may be formed using an amino acid, including specifically, γ Glu.²⁴⁷ The ’483 Publication teaches conjugating the albumin-binding moiety to the side chain of a Lys, including at position 20.²⁴⁸ The ’483 Publication teaches employing a fatty acid chain having 10-24 carbon atoms, and specifically 16 or 18 carbons atoms.²⁴⁹

127. It teaches that maintaining the native amino acid residues at positions 4-6, 8, 12, 18, 25-26 (Gly, Thr, Phe, Ser, Ile, Ala, Trp, Leu) is important to dual

²⁴⁵ EX1008, [0056].

²⁴⁶ EX1008, [0057]-[0058].

²⁴⁷ EX1008, [0063]-[0066].

²⁴⁸ EX1008, [0054], [0064]-[0066] (also listing 16, 17, 19, 24, 27, 28, 30, and 32). Likely recognizing that Lys²⁰ conjugation had become somewhat expected or standardized based on the pattern set with liraglutide, the ’483 Publication asserts that Lys¹⁷ was a non-conservative and non-obvious replacement for the endogenous Ile residue at that position that provided a handle for conjugation to prolong half-life of the peptide and may enhance GLP-1 receptor activity. EX1008, [0022]. This supposition that Lys¹⁷ may be unique in no way renders Lys²⁰ any less obvious.

²⁴⁹ EX1008, [0060]-[0061].

agonist functionality, but that even non-conservative substitutions are permissible at positions 2, 3, 7, 9, 13-15, 17, 19-24, and 27-30 so long as there is an Ile, Gln, Lys, Arg, or Glu in position 17.²⁵⁰

128. The '483 Publication teaches a genus of dual GIP/GLP-1 agonists as SEQ ID NO: 59.²⁵¹ The '483 Publication teaches a smaller genus of dual GIP/GLP-1 agonists as SEQ ID NO: 2.²⁵² With the exception of the Gln at position 24, the entire N-terminal sequence (i.e., residues 1-28) of the dual GIP/GLP-1 agonist in the '657 Publication fits within the express teachings of SEQ ID NO: 59 of the '483 Publication. The same is true of the narrower genus identified by SEQ ID NO: 2, with the sole additional exception that SEQ ID NO: 2 does not expressly identify the Ile at position 27 indicated by SEQ ID NO: 59 and by the GIP/GLP-1 dual agonist in the '657 Publication. As explained above, the '483 Publication teaches that the C-terminal region of the peptide (beginning at residue 29) is expendable or beneficially replaced by the known exenatide C-terminal tail.

129. The '483 Publication teaches use of dual GIP/GLP-1 agonists for the treatment of metabolic disease such as diabetes and obesity, including by reducing

²⁵⁰ EX1008, [0006]-[0007].

²⁵¹ EX1008, [0007].

²⁵² EX1008, [0017].

blood glucose, inducing weight and fat loss, and by reducing high cholesterol.²⁵³

The '483 Publication teaches formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient, including for administration by injection.²⁵⁴ It teaches that formulations and processes for preparing the same are well known in the art.²⁵⁵ It specifically teaches administration in combination therapy, including in combination with metformin, sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, or insulin, and other actives.²⁵⁶

C. WO 2006/097537 A2

130. International Publication No. WO 2006/097537, entitled “ACYLATED GLP-1 COMPOUNDS” (the '537 Publication) published on September 21, 2006, based on applications filed by Novo Nordisk A/S on March 20, 2006, and March 18, 2005. The '537 Publication was identified in December 2014 as providing the structure for semaglutide, the once-weekly GLP-1-receptor agonist in clinical development by Novo Nordisk.²⁵⁷ Accordingly, I have been advised that the '537 Publication is prior art to the '780 patent.

²⁵³ EX1008, [0052], [0071], [0077]-[0078], [0085], Claims 28-36, 45-49.

²⁵⁴ EX1008, [0081], Claims 25-27.

²⁵⁵ EX1008, [0083]-[0084], [0086].

²⁵⁶ EX1008, [0088]-[0090].

²⁵⁷ EX1010 (WO2014/202,727), 1:21-23; EX1009, Example 4.

131. The '537 Publication is directed to protracted duration of action and therapeutic uses of GLP-1 agonists.²⁵⁸ 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.²⁵⁹ 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.²⁶⁰

132. To address that need, the '537 Publication 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.²⁶¹ The '537 Publication 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

²⁵⁸ EX1009, Abstract.

²⁵⁹ EX1009, 1:5-24.

²⁶⁰ EX1009, 1:25-34.

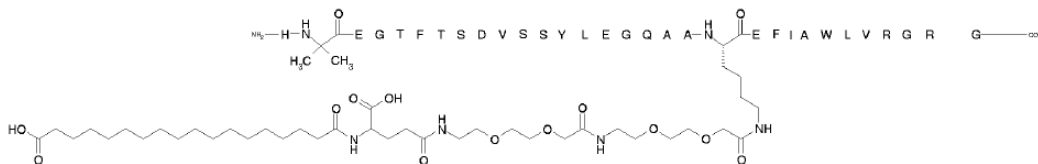
²⁶¹ EX1009, 2:1-4, 10-13.

which remain insulinotropic agents.²⁶² The '537 Publication 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.²⁶³

133. The '537 Publication 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, and a homologue (with 18 methylene units in the fatty acid chain instead of 16) in Example 5.²⁶⁴

Example 4

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



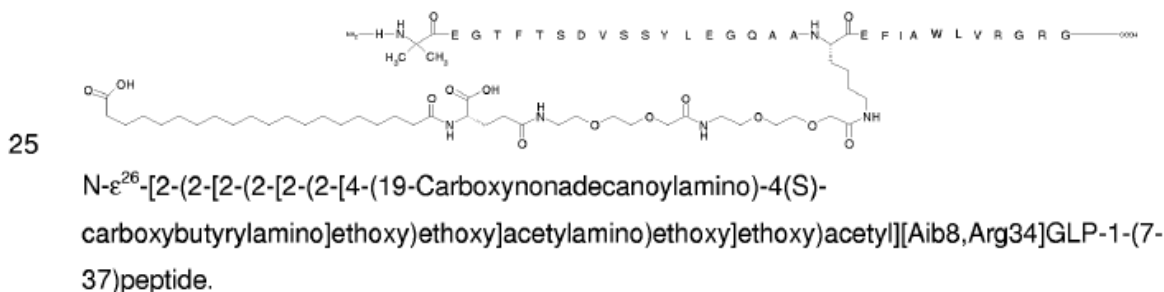
- [Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide
10 synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was

²⁶² EX1009, 3:8-4:8.

²⁶³ EX1009, 6:6-21.

²⁶⁴ EX1009, 47:4-12 (Example 4), 47:12-48:11 (Example 5); *see also* EX1009, 17:1-10, 20:6-9.

Example 5



IX. GROUND 1. CLAIMS 1-7, 9-10, 12-18 WERE OBVIOUS OVER THE '657, '483, AND '537 PUBLICATIONS

134. As set forth below, claim 1 of the '780 patent, from which all other claims depend, recites a genus of peptides following one of two sequences, varying from one another by the identity of one of two residues at position 22 of the peptide (shown in red)²⁶⁵:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
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	

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	I	A	Q	K	A	Nal	V	Q	W	L	I	A	G	G	P	S	S	G	A	P	P	S	S

In each case, the C-terminal amino acid is optionally amidated as a C-terminal primary amide, and the epsilon-amino group of the lysine (K) at position 20 (Lys²⁰) is conjugated to a known albumin-binding substituent (recited as ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)_α-CO-(CH₂)_b-CO₂H, where α = 1 to 2 and b = 10 to 20).

135. As set forth in my analysis below, the prior art (e.g., the '657

²⁶⁵ EX1001, claim 1. Aib is an abbreviation for alpha amino isobutyric acid and Nal or 1-Nal is an abbreviation for (1-naphthyl-alanine). EX1001, 8:35-40.

Publication together with the '483 Publication) teaches or suggests to a POSA that a peptide having the same sequence as is claimed makes a useful GIP/GLP-1 receptor dual agonist, which agonism was associated with glycemic control and weight loss benefits. Moreover, the prior art ('537 Publication) teaches conjugating the claimed albumin-binding moiety to the epsilon-amino of Lys²⁰ to achieve an *in vivo* half-life compatible with dosing frequency of less than once per day (e.g., once-weekly dosing). By January 9, 2015, a POSA thus had good reason to conjugate the claimed albumin-binding moiety to the peptide at Lys²⁰ to make a GIP/GLP-1 receptor agonist with adequate half-life to achieve a dosing frequency of less than once per day (e.g., once-weekly dosing). Both the peptide synthesis and chemical conjugation at issue were very straightforward and well-within the skill of a POSA at the time. Accordingly, a POSA had good reason to make and use compounds falling within the scope of the challenged claims 1-7, 9-10, 12-18 with a reasonable expectation of success.

136. Based on my review of the scope and content of the prior art, the differences between the art and the claims at issue, the level of ordinary skill in the art, and my review of the challenged patent to search for secondary considerations, it is my opinion that making and using these compounds would have been obvious to a POSA by January 9, 2015 without the benefit of the disclosure in the '780 Patent.

137. Additionally, it is my opinion based on the facts of record and my expertise that these compounds having very close structural similarity to prior dual GIP/GLP-1 receptor agonists were likely to share a similar utility with prior dual GIP/GLP-1 receptor agonists. Moreover, the prior art discloses a suitably operative process for making these compounds. Indeed, a POSA would have been motivated with a reasonable expectation of success to make these compounds, consistent with the known structure-activity relationship (“SAR”) for GIP/GLP-1 dual agonism, to provide peptide analogues expected to have GIP/GLP-1 dual agonism properties. Given the known SAR for GIP/GLP-1 agonism, the state of the art was sufficient for a POSA to infer that the structural differences between these compounds and the prior art would preserve GIP/GLP-1 dual agonism utility sufficient to warrant making the new compounds. Indeed, a POSA would have recognized that the similarity between the chemical structures and properties is sufficiently close that a POSA would have been motivated to make and use the claimed compounds.

138. Facial obviousness of the claimed peptide sequence is supported by the expectation of a specific and significant utility (e.g., GIP/GLP-1 dual agonism associated with glycemic control and weight loss). There was a reasonable expectation the compound would have properties similar to the prior art compounds (e.g., GIP/GLP-1 dual agonism associated with glycemic control and weight loss) sufficient to warrant the effort and expense involved in synthesis and

testing of the claimed compound, which was minimal in view of the state of the art.²⁶⁶ I am aware of no prior art teaching away from the claimed compound. Nor am I aware of any reliable evidence (having reviewed the challenged patent in depth) that demonstrates that the claimed compounds possess unexpectedly advantageous or superior properties different in kind from the properties of the closest prior art.

139. In addition to the rationale discussed above, it also is my opinion that a POSA would have identified the peptide based on SEQ ID NO: 1 of the '657 Publication as a lead compound, which is a compound that is a most promising compound for further development and optimization when accounting for its positive and negative qualities. Specifically, a POSA would have recognized that this peptide was a most promising compound because of its known GIP/GLP-1 dual agonist properties that were consistent with the known SAR for GIP/GLP-1 dual agonism, including as described in the '483 Publication. A POSA would have recognized by this same known SAR that the peptide desirably would have been modified or even improved by replacing its non-endogenous C-terminal tail with the known C-terminal motif already used successfully in FDA-approved GLP-1 agonist therapeutics. A POSA similarly would have recognized that the peptide

²⁶⁶ See Section VII.A.2-4 above.

desirably would have been modified or even improved by conjugating the peptide at the epsilon amino of a Lys²⁰ to a prior art albumin-binding substituent already used to improve the *in vivo* half-life of the GLP-1 agonist semaglutide, which achieved a dosing frequency of once-weekly.

140. Ultimately, based on the prior art of record, the claimed compound is the result of combining prior-art elements—e.g., the 28 N-terminal residue operational unit of the peptide in the '657 Publication with the 11-residue exenatide C-terminal motif and Lys²⁰ as disclosed in the '483 Publication, and with the Lys²⁰-conjugated albumin-binding substituent of the '537 Publication—according to known methods to yield predictable results of creating a GIP/GLP-1 receptor dual agonist with increased half-life. This combination similarly substitutes one known element for another to obtain predictable results and uses a known technique (albumin-binding substituent conjugation at the epsilon amino of Lys²⁰) to improve a similar product in the same way to yield predictable results. At a minimum, this combination was obvious to try from among a finite number of identified, predictable solutions for which there was a reasonable expectation of success.

141. My analysis below, on a claim-by-claim basis, identifies exemplary disclosures of the cited references for individual claim elements. This analysis is not meant to be exhaustive. As I set forth in my analysis below, a skilled artisan

would have understood claims 1-7, 9-10, 12-18 to have been obvious in view of the combined teachings of the references asserted herein.

A. Claim 1:

1) Amino Acid Sequence

1. A compound of Formula:

1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39
Y	X ₁	E	G	T	F	T	S	D	Y	S	I	X ₂	L	D	K	I	A	Q	K	A	X ₃	V	Q	W	L	I	A	G	G	P	S	S	G	A	P	P	P	S

Wherein X₁ is Aib

X₂ is Aib...

X₃ is Phe or 1-Nal;

142. The claimed genus of the two peptide sequences is obvious over the '657 Publication in view of the '483 and '537 Publications.

a) A Promising Prior Art GIP/GLP-1 Dual Agonist

143. The '657 Publication discloses a GIP/GLP-1 dual agonist peptide sequence useful for treating diabetes and/or reducing body weight.²⁶⁷

²⁶⁷ EX1007, Abstract, 2:12-25, 5:24-27, Claims 1-12.

The present invention provides a peptide comprising the sequence:

15 Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
5 10
Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa¹-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
20 Xaa²-Xaa³ (SEQ ID NO:1)

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
25 both are optionally PEGylated.

The '657 Publication discloses the GIP/GLP-1 dual agonist peptide sequence as 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.²⁶⁸ The '657 Publication teaches that harnessing GIP agonism together with GLP-1 agonism achieves desirable glucose-lowering and weight-decreasing effects without as much nausea as arises from employing full GLP-1 agonism alone.²⁶⁹

²⁶⁸ EX1007, 2:5-10, 11:20-27, 1:8-21.

²⁶⁹ EX1007, 1:21-23.

144. The '657 Publication provides *in vitro* and *in vivo* data indicating SEQ ID NO: 1 has utility as a GIP/GLP-1 dual agonist, including for glycemic control and weight loss. First, the '657 Publication reports GIP and GLP-1 K_i values for the peptide approaching low picomolar concentrations whether position 22 is occupied by Phe or 1-Nal, but reports that the K_i rises (i.e., affinity decreases) nearly 1000-fold with the addition of C-terminal Cys residues and PEGylation to improve half-life.²⁷⁰ From cellular assays measuring cAMP generation, the '657 Publication teaches that the peptide activated GIP and GLP-1 receptors whether position 22 is occupied by Phe or 1-Nal, with stronger potency values for GIP than GLP-1.²⁷¹ Again, addition of C-terminal cysteines for PEGylation decreased potency.²⁷² The '657 Publication then reports that *in vivo* administration of these less potent PEGylated peptides still resulted in dose-dependent decreases in weight, fat mass, food intake, blood glucose, triglycerides, and cholesterol as compared to vehicle.²⁷³ Based on the disclosures of the '657 Publication, a POSA thus had good reason to make and evaluate structurally similar peptide sequences likely to share the GIP/GLP-1 receptor dual agonism utility of the disclosed SEQ

²⁷⁰ EX1007, 13:7-8 & Table 1 (GIP), 15:1-3 & Table 2 (GLP-1).

²⁷¹ EX1007, 17:1-19:7 & Tables 4-5.

²⁷² In contrast to its potent GIP/GLP-1 binding affinity, the peptide had no selective affinity for glucagon receptor. EX1007, 16:22-23 & Table 3.

²⁷³ EX1007, Tables 6-7, 22:15-30.

ID NO: 1. Additionally, a POSA had good reason to look to SEQ ID NO: 1 as a lead compound for further development and optimization because of its most promising GIP/GLP-1 dual agonism properties and the likelihood that this compound would be favorably improved through further modification.

Claim 1[a]	Prior Art
<p style="text-align: center;">A compound of Formula:</p> $\begin{array}{c} \text{Y X}_1 \text{ E G T F T S} \\ \text{D Y S I X}_2 \text{ L D K} \\ \text{I A Q K A X}_3 \text{ V} \\ \text{Q W L I A G G P} \\ \text{S S G A P P P S;} \end{array}$ <p style="text-align: center;">Wherein</p> <p>X₁ is Aib</p> <p>X₂ is Aib...</p> <p>X₃ is Phe or 1-Nal;</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> Efficacious GIP/GLP-1 receptor dual agonist sequence for treatment of diabetes and obesity:²⁷⁴ <p style="padding-left: 40px;">The present invention provides a peptide comprising the sequence:</p> <div style="margin-top: 10px;"> <pre> sequenceDiagram participant Seq as Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa¹-Val-Gln-Trp-Leu-Ile-Ala-Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln-Xaa²-Xaa³ Note over 1,10: Highlighted Region 1 Note over 11,18: Highlighted Region 2 Note over 19,26: Highlighted Region 3 </pre> <p>15 5 10</p> <p>15 20 25</p> <p> Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln-</p> <p> 30 35 40</p> <p>20 xaa²-xaa³ (SEQ ID NO:1)</p> </div> <p style="margin-top: 20px;">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</p> <p>25 both are optionally PEGylated.</p>

b) Exenatide C-Terminal Motif Useful For GIP/GLP-

²⁷⁴ EX1007, 2:12-25 (claimed sequence residues highlighted in green).

1. Dual Agonists

145. A POSA had very good reason to look to prior art structure-activity-relationship (SAR) information for GIP/GLP-1 dual agonisms to build upon and even improve the peptide sequence from the '657 Publication. In so doing, a POSA would have understood that the first 28 or 29 residues of the peptide constituted the operational section of the peptide, with portions of that operational section serving to cause receptor activation of the core domain and others serving to bind the extracellular NTD.²⁷⁵ In contrast, a POSA would have understood that residues 29-39 were not critical to dual agonist function or selectivity with few exceptions.²⁷⁶

146. The '483 Publication teaches that the C-terminal tail of wild-type GIP (positions 30-42) may be deleted entirely or replaced with the familiar exenatide C-terminal motif.²⁷⁷ As discussed above²⁷⁸, this same motif had been successfully appended to DPP-IV-resistant GLP-1 to improve its potency and metabolic

²⁷⁵ See Section VII.C above.

²⁷⁶ A POSA would have understood that avoiding the glucagon MNT motif at positions 27-29 avoided sacrificing GIP/GLP-1 selectivity in favor of glucagon selectivity. See Section VII.C above.

²⁷⁷ EX1008, [0006], [0024] ("it is believed that a truncation of the C-terminal of native GIP may be performed without affecting the GIP receptor activity. The truncation can be of any length (1-13 amino acids) down to the 29 amino acid GIP peptide."), [0025] ("addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser...at or after position 29 or at or after position 30 of a native GIP or a GIP analogue may increase GLP1 receptor activity."); see also Section VII.B (confirming prior art disclosure sequence of exenatide C-terminal motif).

²⁷⁸ See Section VII.C above.

stability without undue immunogenicity.²⁷⁹

147. The '483 Publication provides SAR data for GIP/GLP-1 dual agonism confirming that favorable dual agonism potency was maintained upon truncation of the peptide (i.e., elimination of residues 30-39 completely) to maintain a length similar to endogenous GLP-1 or by substitution of the C-terminal residues (e.g., beginning at position 29) with the known C-terminal motif GGPSSGAPPPS found in FDA-approved GLP-1 receptor agonist exenatide (derived from natural Gila monster GLP-1 receptor agonist).²⁸⁰ Exenatide's C-terminal motif was associated with reduced clearance mechanisms, some improvement in half-life, and less susceptibility to undesirable DPP-IV cleavage.²⁸¹

148. By sorting the tested peptides potencies below (and juxtaposing them with the sequences of the natural peptides and the FDA-approved GLP-1

²⁷⁹ EX1053, 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.”)

²⁸⁰ As discussed above in Section VIII.B, the operational unit disclosed in the first 28 amino acid residues of SEQ ID NO:1 in the '657 Publication is encompassed within, and entirely consistent with, the SAR for GIP/GLP-1 dual agonism disclosed in the '483 Publication.

²⁸¹ EX1048 (Kieffer), 3587, Figure 1; EX1030 (Donnelly), 28.

comparator liraglutide), I have illustrated GIP/GLP-1 receptor dual agonism SAR of the '483 Publication that would have been understood by a POSA. This SAR is evident regardless of whether one sorts for GIP or GLP-1 receptor agonist activity (see Tables A and B, respectively, below). As illustrated in Tables A and B, truncation or C-terminal GGPSSGAPPPS motif replacement each provided excellent potency consistent with the structural approach in the '657 Publication.

Table A

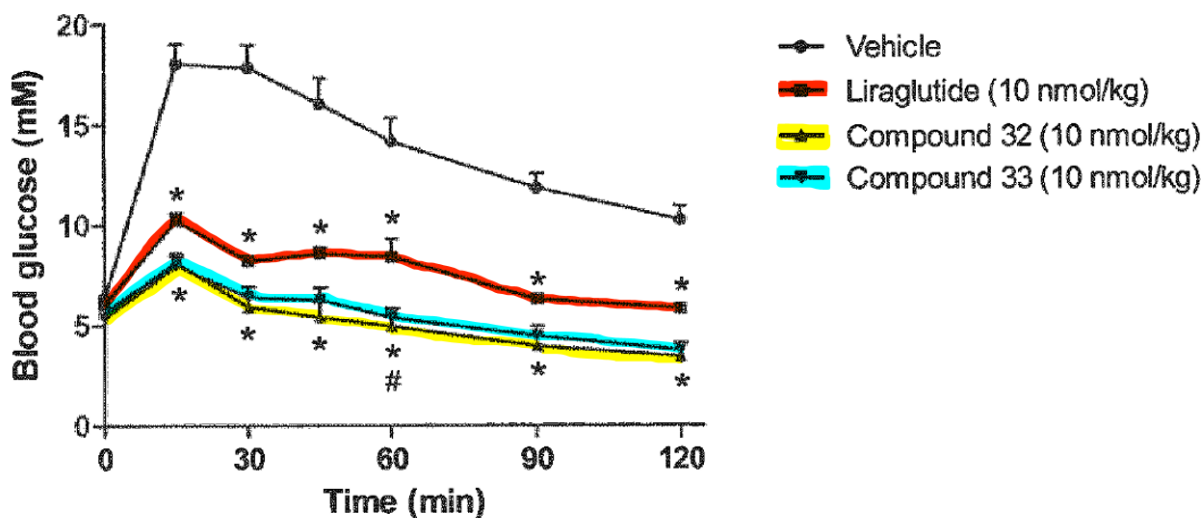
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	GIP	GLP-1
GIP	Y	A	E	G	T	F	T	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
GLP-1	H	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Liraglutide	H	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Exenatide	H	G	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 2	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 55	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 39	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 43	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 37	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 36	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 40	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 32	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 41	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 3	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 19	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 44	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 17	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 31	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 29	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 35	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 5	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 33	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 14	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 54	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 34	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		
Compound 20	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q		

Table B

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40		42		GIP	GLP-1				
GIP	Y	A	E	G	T	F	T	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q							
GLP-1	H	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q							
Liraglutide	H	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q							
Exenatide	H	G	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q							
Compound 28	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.020	0.0051	
Compound 19	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.015	0.0073	
Compound 17	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.021	0.0074	
Compound 24	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.096	0.0085	
Compound 55	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0071	0.0087	
Compound 14	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.036	0.0087	
Compound 29	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.024	0.0088	
Compound 30	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.054	0.0093	
Compound 39	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0083	0.011	
Compound 41	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.013	0.014	
Compound 16	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.053	0.012	
Compound 23	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.42	0.012	
Compound 42	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0070	0.012	
Compound 44	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.016	0.013	
Compound 9	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.091	0.014	
Compound 2	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0068	0.015	
Compound 36	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0099	0.015	
Compound 18	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.36	0.015	
Compound 43	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0091	0.017	
Compound 37	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0097	0.018	
Compound 32	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.012	0.018	
Compound 38	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.0070	0.018	
Compound 40	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.011	0.022	
Compound 3	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.015	0.022	
Compound 35	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.028	0.022	
Compound 5	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.031	0.023	
Compound 7	Y	G	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.21	0.024	
Compound 8	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.10	0.029	
Compound 33	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.035	0.031	
Compound 34	Y	A	E	G	T	F	T	S	D	Y	S	I	A	L	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.045	0.031
Compound 13	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.14	0.032	
Compound 54	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.037	0.033
Compound 48	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.061	0.041
Compound 25	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.12	0.041
Compound 46	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.088	0.048
Compound 49	Y	A	E	G	T	F	T	S	D	Y	S	I	Y	S	D	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	A	A	G	P	S	S	G	A	P	P	P	S	NH2						0.092	0.049

149. The *in vivo* data in the '483 Publication further confirmed that employing the natural C-terminal motif (from exenatide) resulted in favorable efficacy. Even those compounds without the most potent EC₅₀ results achieved superior results in lowering glucose and body weight compared to liraglutide, even using much lower doses.²⁸² For example, even those compounds without the most potent EC₅₀ results (Compound 32, 10 nmol/kg, yellow; Compound 33, 10 nmol/kg, light blue) achieved superior results in lowering glucose compared to liraglutide (10nmol/kg, red), as shown in Figure 1.

Figure 1



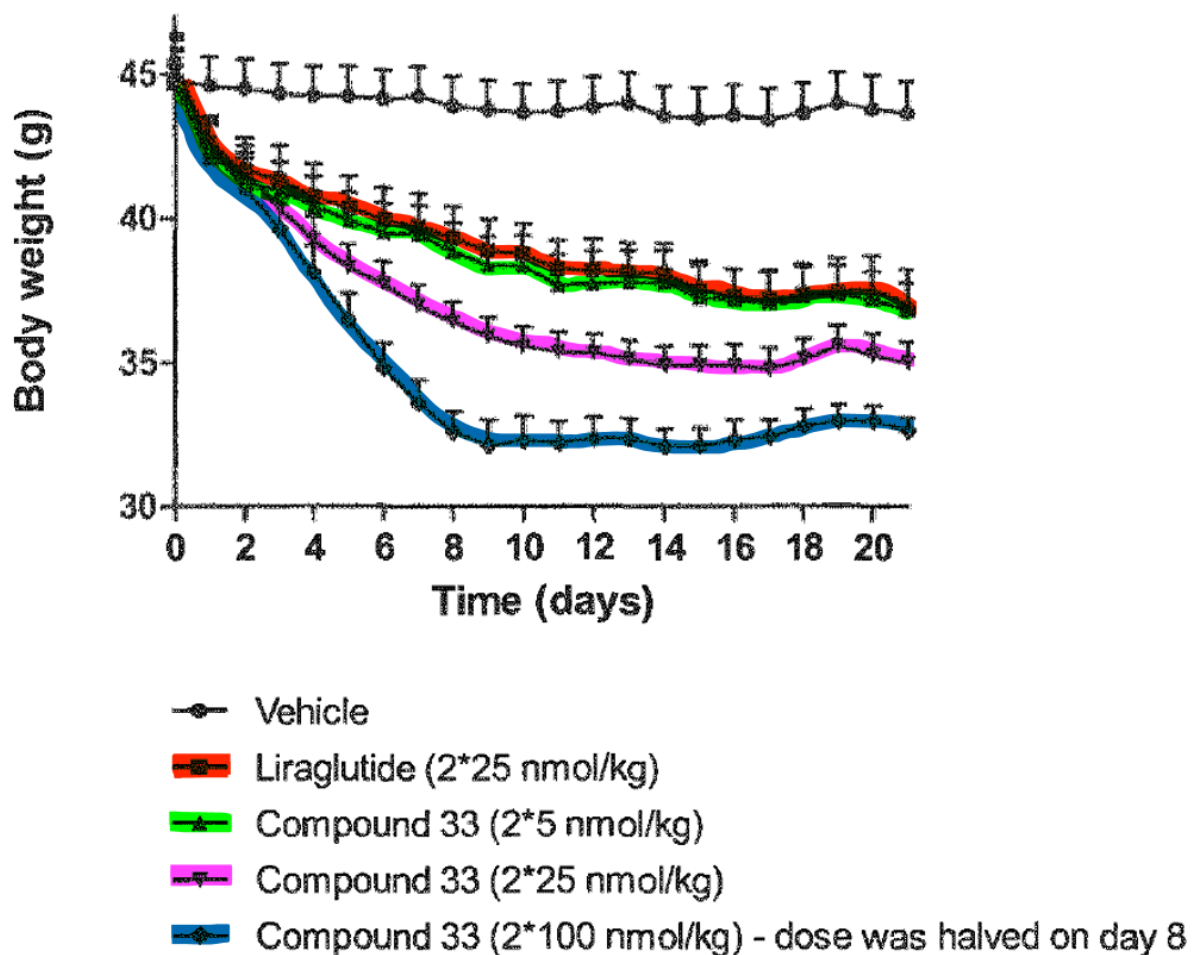
As another example, compound 33 (2*5 nmol/kg, green) achieved comparable body weight reductions to liraglutide (2*25nmol/kg, red) using one-fifth of the dose,

²⁸² EX1008, [0117]-[0119] & Figs. 1-7.

and achieved greater weight reduction with additional dosing (2*25 nmol/kg, magenta; 2*100 nmol/kg, dark blue), as shown in Figure 2.²⁸³ A POSA would have understood that this *in vivo* testing supported efficacy of these compounds as well as of the remaining peptides having comparable or better potencies.

Figure 2:

A



²⁸³ See, e.g., EX1008, Fig. 2.

150. Accordingly, a POSA had good reason in view of the '483 Publication to truncate SEQ ID NO: 1 from '657 Publication after position 29 or to substitute the C-terminal residues beginning at position 29 with exenatide's known C-terminal motif GGPSSGAPPPS,²⁸⁴ to create a compound having GIP/GLP-1 dual-agonism utility without unnecessary and foreign C-terminal amino acid residues.

151. Additionally, a POSA would have recognized that SEQ ID NO: 1 unnecessarily employs a non-natural Aib residue at position 29 and a long C-terminal motif that does not appear in any of the natural ligands or the FDA-approved therapeutic ligands. Though perhaps useful to Lilly to stake out some claim to novelty for the synthetic peptide, a POSA would have recognized that this unnatural sequence was potentially undesirable as it raised the risk of high immunogenicity and the elicitation of anti-drug antibodies, but was not required for excellent efficacy. A POSA would have recognized that replacing SEQ ID NO: 1's unnatural C-terminal residues 29-39 with exenatide's natural C-terminal GGPSSGAPPPS²⁸⁵ motif provided the additional benefit of avoiding a likely source of unnecessary immunogenicity, and anti-drug antibodies, which are known to reduce efficacy of peptide based drugs. A POSA would have recognized that the prior art substitution would avoid unnecessary use of the non-natural (and

²⁸⁴ EX1069 (Thum), Abstract, 7-8.

²⁸⁵ *Id.*

potentially immunogenicity-inducing) Aib at position 29 by employing the Gly found naturally in endogenous and synthetic FDA-approved GLP-1 receptor agonists exenatide and liraglutide, which are known to elicit low-titer anti-drug antibodies consistent with therapeutic efficacy.²⁸⁶

152. 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.²⁸⁷ Accordingly, an expectation of reduced unnecessary immunogenicity²⁸⁸ as compared to SEQ ID NO: 1 provided a POSA with additional very good reason to apply the prior art exenatide C-terminal motif to the prior art dual agonist disclosed in the '657 Publication.²⁸⁹

²⁸⁶ EX1009, 47:4-28, (providing endogenous sequence for 31-residue version of GLP-1 with G at position 29), 4:1-2 (defining GLP-1), 4:32-5:3 (invoking 39-residue sequence of Exendin-4); EX1053, 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).

²⁸⁷ See Section VII.B-C above.

²⁸⁸ EX1053, 9; EX1054, 14.

²⁸⁹ The '657 Publication recognized the goal of avoiding undesirable protease cleavage. Apparently references its use of Aib residues at position 2 and 13, which substitutions were known to prevent DPP-IV-catalyzed and activity-defeating

153. The fact that excellent *in vivo* potency was observed in the '483 Publication did more than merely confirm that both truncation and C-terminal motif replacement would work in SEQ ID NO: 1 of the '657 Publication for making the dual agonist. It also demonstrated that both approaches (truncation or C-terminal motif replacement) were either (1) sufficient to achieve adequate selectivity against glucagon receptor agonism to achieve excellent therapeutic results; or (2) suitable for achieving excellent therapeutic results despite whatever level of glucagon receptor agonism might have been achieved.²⁹⁰ In light of the successful results of the '483 Publication in eliminating the unnecessary C-terminal amino acid residues in SEQ ID NO: 1, and in view of ongoing work with GLP-1/glucagon receptor dual agonism for treatment of obesity and diabetes, a POSA would not have been dissuaded or discouraged from truncation or C-terminal motif substitution by any concerns about GCGR agonism.

154. In addition to understanding that C-terminal truncation or exenatide-tail substitution of SEQ ID NO: 1 was consistent with obtaining efficacy and utility, a POSA further would have understood that the '483 Publication's SAR

peptide cleavage, the '657 Publication teaches SEQ ID NO:1 is less susceptible to rapid metabolic deactivation by DPP-IV. EX1007, 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 the '483 Publication, but also is consistent with scientific goals of the '657 Publication.

²⁹⁰ EX1069 (Thum), Abstract, 7-8.

confirmed that the peptide sequence of residues 1-28 of SEQ ID NO: 1 was favorable for an efficacious GIP/GLP-1 receptor dual agonist. Table C below places the amino acid residues of SEQ ID NO: 1 in context with the '483 Publication SAR, the natural ligands, and FDA-approved liraglutide, to illustrate the consistency of the first 28 amino acid residues known to be the operative portion of the peptide for GIP/GLP-1 receptor dual agonism.²⁹¹

Table C

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42		
WO 2011/119657	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	I	A	Q	R	A	For Nat	V	Q	W	L	I	A	Aib	K	K	Q	K	K	H	Q	I	T	Q					
GIP	Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	L	A	Q	K	K	G	K	K	N	D	W	K	H	N	I	Cor N/A	Cor N/A	
GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R	G	NH2												
Liraglutide	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K**	E	F	I	A	W	L	V	R	G	R	G													
Exenatide	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 2	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 55	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 39	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	K	E	F	V	E	W	L	L	S	A	NH2														
Compound 43	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	E	W	L	L	S	A	NH2														
Compound 37	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2														
Compound 36	Y	Aib	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K**	A	Q	R	A	F	V	N	W	L	V	A	Aib	K	P	S	S	G	A	P	P	P	S	NH2				
Compound 40	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2														
Compound 32	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 41	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2														
Compound 3	Y	Aib	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	I	A	Q	R	A	F	V	N	W	L	V	A	Aib	K	NH2													
Compound 19	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	K	E	F	V	N	W	L	L	A	Aib	K	NH2													
Compound 44	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	NH2														
Compound 17	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2													
Compound 31	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K*	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2													
Compound 29	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 35	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	P	S	S	G	A	P	P	P	S	NH2				
Compound 5	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2													
Compound 33	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K**	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 14	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2													
Compound 54	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K**	A	A	K	E	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 34	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	E	F	I	E	W	L	E	S	A	NH2														
Compound 20	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	K	W	L	L	A	Aib	K	NH2													

²⁹¹ Apparently referring to Aib residues at positions 2 and 13 known to prevent DPP-IV-catalyzed and activity-defeating peptide cleavage, the '657 Publication teaches the peptide is less susceptible to rapid metabolic deactivation by DPP-IV. EX1007, 5:22-23. Exenatide's C-terminal GGPSSGAPPPS motif provided the additional benefit of avoiding the non-natural Aib at position 29 by employing the G found naturally in endogenous and synthetic FDA-approved GLP-1 receptor agonists. A POSA would have understood that G was less susceptible to DPP-IV cleavage than A but less immunogenic than the non-natural Aib residue.

155. Aside from the C-terminal tail (beginning at residue 29), the '657 Publication peptide sequence differs from amino acid residue positioning disclosed in the '483 Publication working examples only at positions 24 (Q) and 27 (I). Nonetheless, the use of these residues at these positions is supported by the disclosure of the '483 Publication.²⁹² For example, the '483 Publication SAR demonstrates that position 24 accommodates each of E (Glu) and N (Asn). These amino acids 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).²⁹³ Despite these differences, the additional methylene is tolerated at position 24. In some circumstances, these differences can impact the function of a peptide significantly. But here, these two amino acid residues are highly interchangeable for GIP/GLP-1 receptor dual agonism.²⁹⁴ That is a strong indication that the function of the peptide permits employing another amino acid residue with consistent side chain structure and functional group.

²⁹² As explained in Section VIII.B above, the 28-residue sequence in the '657 Publication is encompassed by and fully consistent with the express disclosures of the GIP/GLP-1 receptor dual agonisms SAR in the '483 Publication.

²⁹³ EX1012, Fig. 5-5 (reproduced in part below).

²⁹⁴ EX1008, [0049]-[0050].

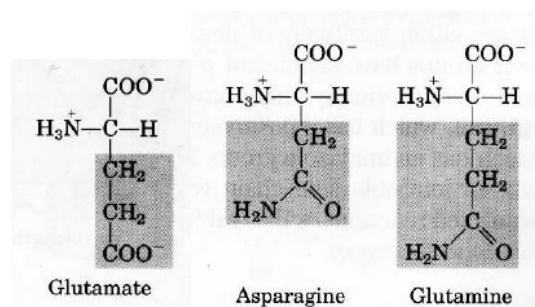


Figure 14.²⁹⁵

156. Consistent with what was known of the structures of the GIP/GLP-1 receptors and their interactions with GIP and GLP-1 for binding and activation²⁹⁶, and the '483 Publication SAR, a POSA would have recognized position 24 was similarly likely to accommodate a Q (Gln, glutamine) amino acid residue because the structure and properties of its side chain are consistent with those of glutamate (Glu, E) and asparagine (Asn, N). For example, the success employing the Glu residue (which appears naturally in exenatide) indicates that the presence of two methylene units in the side chain (extending steric bulk physically further away from the backbone) did not impair excellent dual agonism. Indeed, all of the five compounds with most potent EC₅₀ for GIPR (and 8 of the 10 most potent) employed E at position 24 while retaining excellent potency for GLP-1R. This was consistent with known ligand-receptor binding information²⁹⁷, which indicated

²⁹⁵ EX1014, 119, Fig. 5-5.

²⁹⁶ See section VII.C above

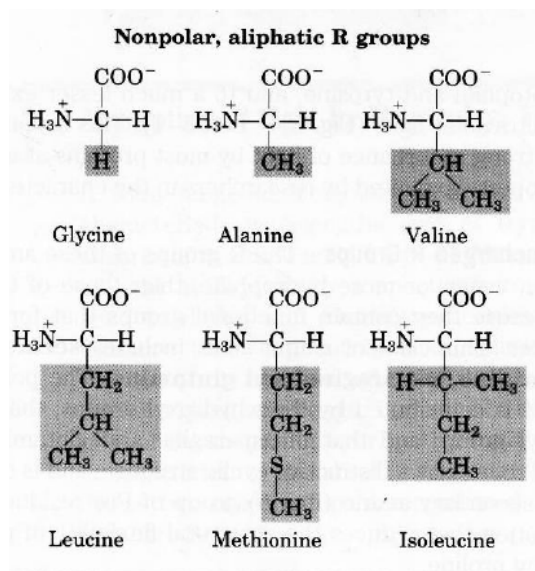
²⁹⁷ See Section VII.C above.

these residues of the ligand were not required to interact directly with the hydrophobic face of the receptor. Similarly, the success employing the Asn residue (which appears naturally in GIP) indicates that neither the additional methylene unit in the side chain nor the charged functional group are required for excellent dual agonism. Accordingly, a POSA would have understood that position 24 would accommodate the use of glutamine (Gln, Q) for making a GIP/GLP-1 receptor dual agonist with excellent potency. Indeed, the '483 Publication discloses that Q is a conservative substitution within its SAR for both E and N.²⁹⁸ Accordingly, the SAR of the '483 Publication is fully supportive of the '657 Publication's use of Q at position 24 to make a potent GIP/GLP-1 dual agonist.

157. The '483 Publication similarly corroborates the disclosure of the '657 Publication of successfully employing isoleucine (Ile, I) at position 27. The '657 Publication discloses that position 27 accommodates each of L or V. These amino acids are sterically and chemically homologous to isoleucine (I). As illustrated by the structures of the proteinogenic nonpolar aliphatic amino acid residues as depicted in Fig. 5-5 of EX1014, valine demonstrates that both GIPR and GLP-1R accommodate the b-branched structure that is also present in isoleucine. Leucine demonstrates that both GIPR and GLP-1R accommodate a further elongation of the

²⁹⁸ EX1008, [0049]-[0050].

amino acid sidechain. Accordingly, a POSA would have recognized position 27 was similarly likely to accommodate the I amino acid residue because the structural and chemical properties of its side chain are similar to those of L and V. Indeed, the '483 Publication expressly discloses the use of I at position 27.²⁹⁹ This also was consistent with what was known about structural information of the receptor-ligand interactions.³⁰⁰ Based on SAR data showing that both leucine and valine were accepted at position 27, a POSA would have accepted the '483 Publication's teaching that SEQ ID NO: 1's isoleucine (Ile, I) would work quite well at that position.³⁰¹



²⁹⁹ See, e.g., EX1008, [0007].

³⁰⁰ See Section VII.C above.

³⁰¹ The '483 Publication also expressly discloses that I is a conservative substitution within its SAR for both L and V. EX1008, [0049]-[0050].

Figure 15.³⁰²

158. Accordingly, the SAR of the '483 Publication confirms that amino acid sequence of residues 1-28 of SEQ ID NO: 1 in the '657 Publication was expected to be operational and efficacious for GIP/GLP-1 receptor dual agonism, whether truncated or employing the exenatide C-terminal GGPSSGAPPPS motif.

³⁰² EX1014, 119, Fig. 5-5.

Claim 1[a]	Prior Art																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
<p>A compound of Formula: Y X₁ E G T F T S D Y S I X₂ L D K I A Q K A X₃ V Q W L I A G G P S S G A P P P S;</p> <p>Wherein X₁ is Aib</p> <p>X₂ is Aib...</p> <p>X₃ is Phe or 1-Nal;</p>	<p>The '483 Publication teaches:</p> <ul style="list-style-type: none">Truncating GIP/GLP-1 dual agonist peptide at residue 29 or replacing distal residues with C-terminal exenatide motif makes efficacious GIP/GLP-1 receptor dual agonists for treatment of diabetes and obesity. <p>“More particularly, preferred GIP analogues of the present inventio comprise...substitution or deletion of one or more of amino acids corresponding to positions 30 to 42 of the wild-type GIP sequence.”³⁰³</p> <p>“[I]t is believed that a truncation of the C-terminal of native GIP may be performed without affecting the GIP receptor activity. The truncation can be of any length (1-13 amino acids) down to the 29 amino acid GIP peptide.”³⁰⁴</p> <p>“[T]he addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser... at or after position 29 or at or after position 30 of a native GIP or a GIP analogue may increase GLP1 receptor activity.”.³⁰⁵</p> <p>Data From EX1008, [0109], [0115], Tables 1, 3 (GIP Sort)</p> <table><tr><th></th><th>1</th><th>2</th><th>3</th><th>4</th><th>5</th><th>6</th><th>7</th><th>8</th><th>9</th><th>10</th><th>11</th><th>12</th><th>13</th><th>14</th><th>15</th><th>16</th><th>17</th><th>18</th><th>19</th><th>20</th><th>21</th><th>22</th><th>23</th><th>24</th><th>25</th><th>26</th><th>27</th><th>28</th><th>29</th><th>30</th><th>31</th><th>32</th><th>33</th><th>34</th><th>35</th><th>36</th><th>37</th><th>38</th><th>39</th><th>40</th><th>41</th><th>42</th><th>GIP</th><th>GLP-1</th></tr><tr><td>GIP</td><td>A</td><td>A</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>GLP-1</td><td>A</td><td>A</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Exenatide</td><td>A</td><td>A</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 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17</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 31</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 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5</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 33</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 14</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 54</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 34</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr><tr><td>Compound 20</td><td>Aib</td><td>E</td><td>S</td><td>T</td><td>P</td><td>T</td><td>S</td><td>D</td><td>V</td><td>L</td><td>E</td><td>K</td><td>A</td><td>Q</td><td>K</td><td>A</td><td>V</td><td>N</td><td>W</td><td>L</td><td>S</td><td>A</td><td>D</td><td>S</td><td>P</td><td>S</td><td>S</td><td>G</td><td>A</td><td>P</td><td>P</td><td>S</td><td>NH2</td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td><td></td></tr></table> <p>Data From EX1008, [0109], [0115], Tables 1, 3 (GLP-1 Sort)</p>		1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	GIP	GLP-1	GIP	A	A	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												GLP-1	A	A	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Exenatide	A	A	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 2	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 55	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 39	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 43	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 37	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 36	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2												Compound 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Compound 36	Aib	E	S	T	P	T	S	D	V	L	E	K	A	Q	K	A	V	N	W	L	S	A	D	S	P	S	S	G	A	P	P	S	NH2																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																																		
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[illegible]

³⁰³ EX1008, [0006].

³⁰⁴ EX1008, [0024]

³⁰⁵ EX1008, [0025].

Figure 1

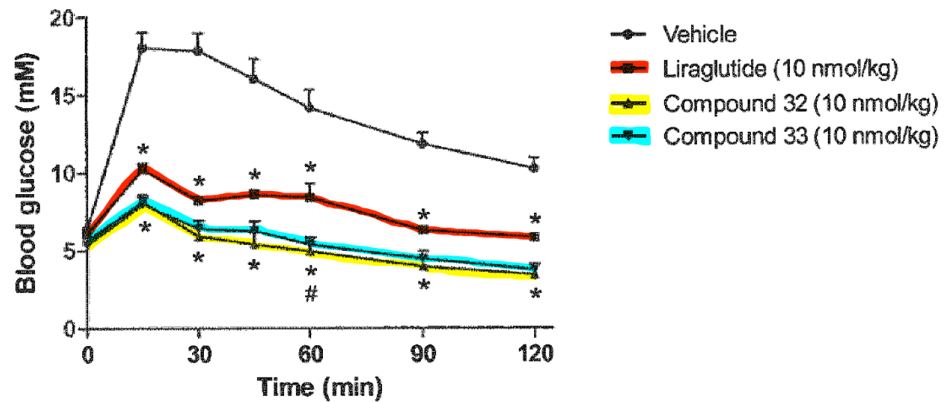
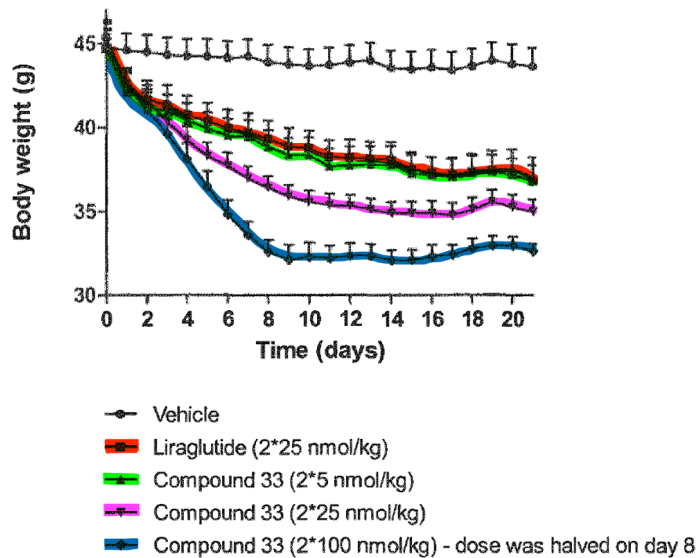


Figure 2:

A



- GIP, GLP-1, and GLP-1 receptor agonists liraglutide (VictozaTM) and exenatide (ByettaTM, BydureonTM) all were known, and dual agonism was desirable.

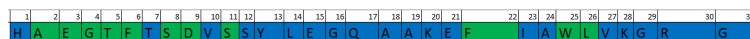
“To date there are two **known incretins**: glucagon-like peptide

(GLP-1), and glucose-dependent insulinotropic polypeptide (GIP)....**GLP-1** is produced as a **37-amino acid peptide that corresponds to amino acids 72 through 108 of pro-proglucagon**. **GIP is a 42-amino acid peptide** derived by proteolytic processing from a 133-amino acid precursor, pre-pro-GIP....[I]njectable GLP-1 receptor agonists...are now on the market (GLP-1 receptor agonists: **Byetta™**, **Bydureon™** and **Victoza™**....[T]he combination of the GLP-1 receptor agonist **Liraglutide** and GIP showed superior glucose-lowering and insulinotropic effects compared to treatment with Liraglutide and GIP alone[.]”³⁰⁶

“Chronic treatment with GLP-1 receptor agonists causes significant weight loss in diabetic humans....Evidence suggests...that body weight loss associated with GLP-1 agonist treatment is enhanced **when GLP-1 and GIP are co-administered**. In rodents, co-administration of GLP-1 and GIP results in greater body weight loss than GLP-1 treatment alone. Thus, in addition to **improving blood glucose control**, GIP may also **enhance GLP-1 mediated body weight loss**.”³⁰⁷

The '537 Publication teaches:

- Amino acid sequence of active GLP-1(7-37 of pro-peptide)³⁰⁸ is



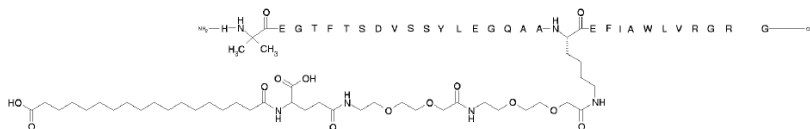
³⁰⁶ EX1008, [0002]-[0003].

³⁰⁷ EX1008, [0004].

³⁰⁸ EX1009, 47:4-28.

Example 4

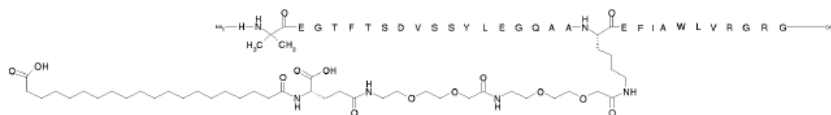
- 5 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



- [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]acetyl)amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



“The term ‘analogue’ as used herein referring to a polypeptide means a modified peptide wherein one or more amino acid residues of the peptide have been substituted by other amino acid residues and/or wherein one or more amino acid residues have been deleted from the peptide and or wherein one or more amino acid residues have been added to the peptide....A simple system is often used to describe analogues: For example [Arg³⁴]GLP-1(7-37)Lys designates a GLP-1(7-37) analogue wherein the **naturally occurring lysine at position 34** [activated peptide position 28] has been substituted with arginine and wherein a lysine has been added to the terminal amino acid residue, i.e. to the Gly³⁷ [terminal Gly in the activated peptide].”³⁰⁹

“The term ‘GLP-1 peptide’ as used herein means **GLP-1(7-37) (SEQ ID NO: 1)**, a GLP-1(7-37) analogue, a GLP-1(7-37)

³⁰⁹ EX1009, 3:8-17.

	<p>derivative or a derivative of a GLP-1(7-37) analogue.”³¹⁰</p> <ul style="list-style-type: none"> • Amino acid sequence of Exendin-4 (exenatide) was known. <p>“The DPP-IV enzyme in plasma is known to be involved in the degradation of several peptide hormones, e.g. GLP-1, GLP-2, Exendin-4[1-39] etc.”³¹¹</p>
--	---

c) Lys²⁰

159. The '537 Publication presents Lys²⁰ as a favorable location for conjugation to an albumin-binding moiety to provide a longer *in vivo* duration of action to insulintropic agents generally and GLP-1 agonists in particular.³¹² Consistent with this disclosure of Lys²⁰ on GLP-1 agonist peptides, the SAR for the '483 Publication specifically confirms that Lys²⁰ works well for GIP/GLP-1 receptor dual-agonists.³¹³ Though the authors readily and successfully created dual agonists using an arginine or histidine at that location as well as using Lys²⁰, the SAR thus suggests the receptors are unlikely to interact specifically with the ligand

³¹⁰ EX1009, 4:1-2.

³¹¹ EX1009, 4:32-5:3; *see also* Section VII.B above.

³¹² EX1009, 1:5-24, 2:10-13, 3:8-4:8, 6:6-21.

³¹³ Several very potent dual-agonists employed Lys²⁰, as illustrated in the SAR chart above.

at that location and are very amenable to Lys²⁰.³¹⁴

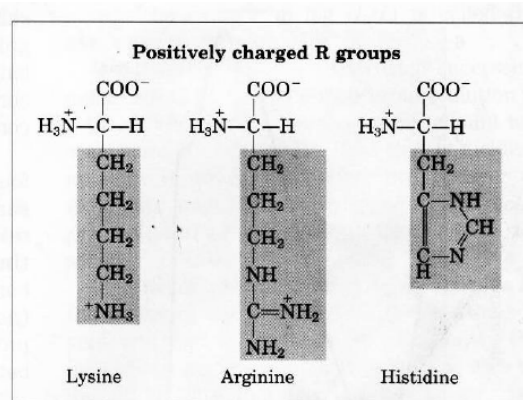


Figure 16.³¹⁵

160. Indeed, Lys²⁰ is employed naturally in GLP-1, as well as in liraglutide, where that therapeutic is acylated to improve that peptide's half-life.³¹⁶

161. Like the '537 Publication, the '483 Publication also specifically identifies Lys²⁰ as a location for conjugation, but for GIP/GLP-1 receptor dual agonist peptides.³¹⁷ The '483 Publication discloses that conjugation of dual agonist

³¹⁴ See portion of EX1014, Fig. 5-5 reproduced below.

³¹⁵ EX1014, 119, Fig. 5-5.

³¹⁶ EX1009, 3:8-17 (providing endogenous sequence for 31-residue version of GLP-1 with K at position 20); EX1009 (liraglutide acylated at Lys²⁰).

³¹⁷ EX1008, [0064]-[0067].

peptides at the epsilon amino of lysine improves the half-life of the peptide.³¹⁸ The '483 Publication explains "it is thought that the lipophilic substituent [conjugated to an amino acid side chain] 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" and "modulate the potency of the compounds, e.g., with respect to the GIP receptor and/or the GLP-1 receptor."³¹⁹ It teaches embodiments where "only one amino acid side chain is conjugated to a lipophilic substituent," and teaches the use of γ Glu spacers between that amino acid and a lipophilic fatty acid chain comprising between 10-24 carbon atoms.³²⁰ Accordingly, employing Lys²⁰ in the peptide is consistent both with the SAR of the '483 Publication and with its express suggestion to acylate GIP/GLP-1 receptor dual agonists at Lys²⁰.

162. In view of common prior art usage of Lys²⁰ for conjugation, the disclosures of the '537 Publication and the '483 Publication, a POSA had good reason with reasonable expectation of success to make a peptide having an amino acid sequence falling within the scope of claim 1 (shown below with comparison to the natural and FDA-approved ligands).

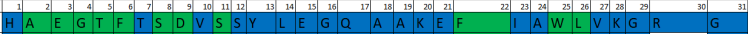
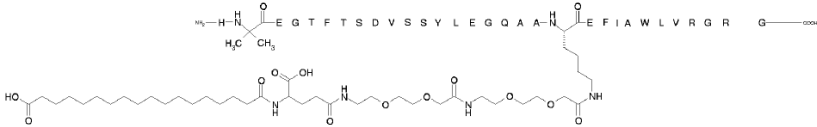
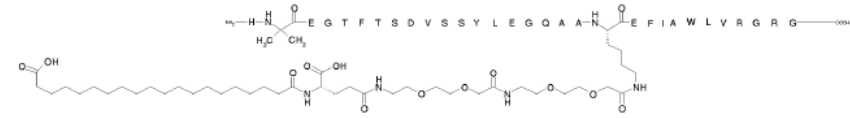
³¹⁸ EX1008, [0006].

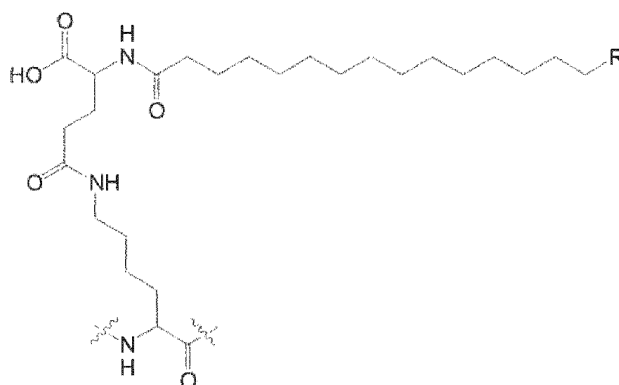
³¹⁹ EX1008, [0056].

³²⁰ EX1008, [0057]-[0058], [0060]-[0061], [0063]-[0066].

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21		22	23	24	25	26	27	28	29		30		31	32	33	34	35	36	37	38	39	
	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	I	A	Q	R	A		F	or	Nal	V	Q	W	L	I	A	G	G		P	S	S	G	A	P	P	P	S

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	
GIP	Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	Q	Q	D	F		V	N	W	L	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q
GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F		I	A	W	L	V	K	G	R	G	NH2										
Liraglutide	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K**	E	F		I	A	W	L	V	R	G	R	G											
Exenatide	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	E	A	V	R	L	F		I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2		

Claim 1[a]	Prior Art
<p>A</p> <p>compound of</p> <p>Formula:</p> <p>Y X₁ E G T F T S D Y S I X₂ L D K I A Q K A X₃ V Q W L I A G G P S S G A P P P S;</p> <p>Wherein</p> <p>X₁ is Aib</p> <p>X₂ is</p> <p>Aib...</p> <p>X₃ is</p> <p>Phe or 1-Nal;</p>	<p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> • Use of Lys²⁰ to facilitate conjugation.³²¹  <p>Example 4</p> <p>5 N-ε²⁶-[2-(2-[2-(2-[2-(4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p>  <p>[Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide</p> <p>10 synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was</p> <p>Example 5</p>  <p>25 N-ε²⁶-[2-(2-[2-(2-[2-(4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> • Use of Lys²⁰ to facilitate conjugation to albumin-binding moiety. <p>“The amino acid side chain to which the lipophilic substituent is conjugated...may be a side chain of a Lys, Glu or Cys residue.”³²²</p> <p>“An example of a lipophilic substituent comprising a lipophilic moiety Z¹ and spacer Z² is shown in the formula below:</p>



Here, the side chain of a **Lys residue** is covalently attached to a γ Glu spacer (Z^2) via an amide linkage.”³²³

“In certain embodiments, a GIP analogue of the invention is conjugated with a lipophilic substituent to one or more amino acid **positions** 16, 17, 19, **20**, 24, 27, 28, 30 and 32.”³²⁴

“More particularly, **preferred GIP analogues of the present invention** comprise non-conservative substitutions at one or more of amino acid positions 1, 2, 3, 7, 9, 13, 14, 15, 17, 19, 20, 21, 22, 23, 24, 27, 28, 29, and 30 of the wild-type GIP sequence in combination Ile, Gln, Lys, Arg or Glu in position 17, optionally in combination with further conservative or non-conservative substitutions at one or more of amino acid positions 10, 11, and 16; and **acylation of one or more of amino acid positions** 15, 16, 17, 19, **20**, 24, 27, 28 and 30....”³²⁵

³²¹ EX1009, 47:4-28.

³²² EX1008, [0064].

³²³ EX1008, [0065]-[0066].

³²⁴ EX1008, [0067].

³²⁵ EX1008, [0006]; *see also* SAR Tables above showing dual agonism activity was very amenable to Lys²⁰ found naturally in GLP-1 and in liraglutide.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42
GLP	Y	A	G	S	T	P	T	S	D	Y	S	A	M	D	K	T	H	R	Q	D	F	V	N	W	L	L	A	G	K	R	K	N	G	W	K	H	N	I	T	Q		
GLP-1	Y	A	G	S	T	P	T	S	D	Y	S	A	M	D	K	T	H	R	Q	D	F	V	N	W	L	L	A	G	K	R	K	N	G	W	K	H	N	I	T	Q		
Liraglutide	Y	A	G	S	T	P	T	S	D	N	S	T	L	E	G	Q	A	A	E	F	V	A	W	L	V	K	S	R	G	NH2												
Exenatide	Y	G	G	T	P	T	S	D	L	S	A	Q	M	E	E	A	V	R	L	F	C	W	L	K	N	S	G	P	S	S	G	A	P	P	P	S	NH2					

2) Albumin-Binding Substituent

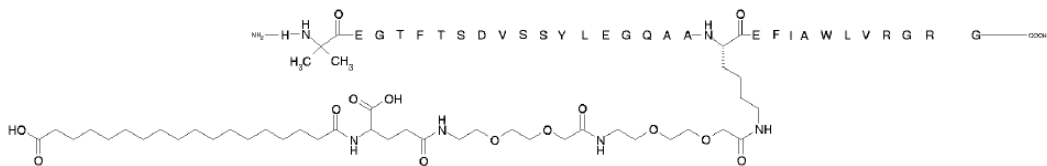
...K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)α-CO-(CH₂)_b-CO₂H wherein α is 1 to 2 and b is 10 to 20...

163. The '537 Publication discloses the claimed albumin-binding substituent. In particular, it discloses chemically modifying Lys²⁰ through conjugation of the albumin-binding substituent ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆₋₁₈-CO₂H to the epsilon-amino group of the Lys²⁰ sidechain. For illustrative purposes, Examples 4 and 5 disclose chemically modifying Lys²⁰ of the GLP-1 receptor agonist semaglutide through conjugation of the albumin-binding substituent ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆₋₁₈-CO₂H to the epsilon-amino group of the Lys²⁰ sidechain.³²⁶ In the Example 4 homologue, the number of methylene units (b) is 16 and in Example 5 it is 18. Both of these albumin-binding substituents satisfy the albumin-binding substituent limitation of claim 1, including with respect to the location and manner of attachment to the peptide.

³²⁶ EX1009, 47:4-12 (Example 4), 47:12-48:11 (Example 5); *see also* EX1009, 17:1-10, 20:6-9.

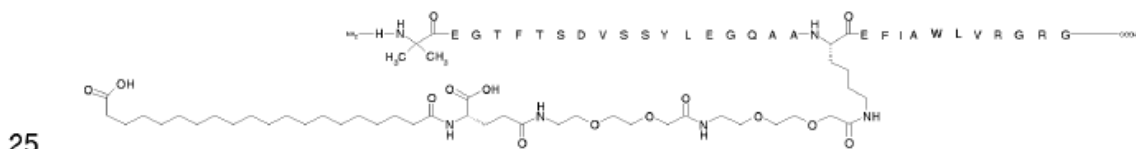
Example 4

- 5 N- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]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- ϵ^{26} -[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

164. A POSA would have had good reason to employ the prior art albumin-binding substituent of the '537 Publication on the amino acid sequence rendered obvious by the '657 and '483 Publications discussed above to improve protracted duration of action to the peptide. A POSA had good reason to accomplish this by conjugating the albumin-binding substituent to the epsilon amino group of Lys²⁰ as disclosed in both the '537 and '483 Publications.³²⁷

165. The '537 Publication teaches that it is desirable to reduce dosing frequency of peptides for the treatment of diabetes and obesity because many

³²⁷ EX1009, 2:1-4.

patients find injections unpleasant.³²⁸ The '537 Publication presents Lys²⁰-conjugation of the albumin-binding moiety as a favorable approach for providing a longer *in vivo* duration of action to insulintropic agents generally and GLP-1 agonists in particular, and explains that the moiety associates the peptide with blood components, such as serum albumin in the patient, to extend *in vivo* half-life.³²⁹ In the case of semaglutide, the albumin-binding-moiety conjugation resulted in once-weekly dosing.³³⁰ This same albumin-binding moiety routinely increased the half-life of GIP/GLP-1 agonists comprising the exenatide C-terminal motif, successfully achieving half-lives similar or longer than that of semaglutide.³³¹ In contrast, using just the fatty acid and γ Glu linker but without using the full linker of the '537 Publication achieved a half-life of 3.4-3.7 hours in mice.³³² A POSA thus would have had good reason with a reasonable expectation of success to use the albumin-binding substituent that achieved protracted duration of action for semaglutide to achieve once-weekly dosing of the GIP/GLP-1 receptor dual

³²⁸ EX1009, 1:25-34.

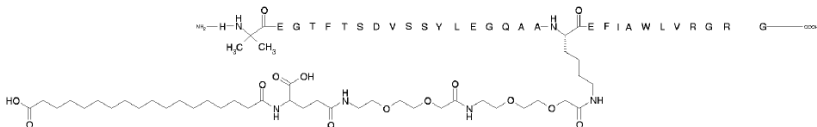
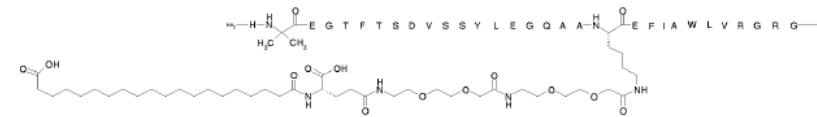
³²⁹ EX1009, 1:5-24, 2:10-13, 3:8-4:8, 6:6-21.

³³⁰ *See, e.g.*, EX1010, 1:21-23; EX1009, Example 4.

³³¹ EX1075 (WO 2015/067,715), Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51 (Table 1), 58 (Table 4).

³³² EX1008, [0116] (Table 4).

agonist, or at least improve its protracted duration of action to be comparable to liraglutide, exenatide, or other prior art GLP-1 receptor agonists.³³³

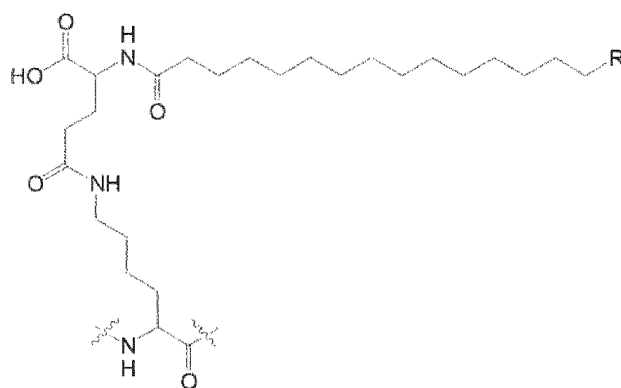
Claim 1[b]	Prior Art
<p>...K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)α-CO-(CH₂)_b-CO₂H wherein α is 1 to 2 and b is 10 to 20...</p>	<p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁-CO-(CH₂)₁₆₋₁₈-CO₂H. <p>Example 4</p> <p>5 N-ϵ^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p>  <p>[Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide</p> <p>10 synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was</p> <p>Example 5</p>  <p>25 N-ϵ^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p> <p>The '483 Publication teaches:</p>

³³³ See Section VII.B.2 above.

- “[I]t is thought that the lipophilic substituent [conjugated to an amino acid side chain] **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. The lipophilic substituent may also modulate the potency of the compounds, e.g., with respect to the GIP receptor and/or the GLP-1 receptor.”³³⁴

- “The lipophilic substituent may include a **hydrocarbon chain having 10 to 24 carbon (C) atoms....**Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³³⁵

“An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:



³³⁴ EX1008, [0056].

³³⁵ EX1008, [0061].

³³⁶ EX1008, [0064].

³³⁷ EX1008, [0065]-[0066].

3) Optional C-terminal Primary Amide

...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.

166. Both the '657 and '483 Publications disclose the C-terminal amino acid is amidated as a C-terminal primary amide.³³⁸ The '483 Publication also disclose the use of pharmaceutically acceptable salts of the peptides.³³⁹

³³⁸ EX1007, 2:23-31 (“the C-terminal amino acid is optionally amidated”); EX1008, 65-67 (Table 1 showing compounds with C-terminal primary amide).

³³⁹ EX1008, [0081] (“salts or solvates thereof, in a pharmaceutically acceptable carrier”), [0084] (“pharmaceutically acceptable salt”). Accordingly, this element is satisfied by the prior art.

Claim 1[c]	Prior Art																																																
<p>...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.</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> The C-terminal amino acid is optionally amidated. <p>“[T]he C-terminal amino acid is optionally amidated[.]”³⁴⁰</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> GIP/GLP-1 receptor dual agonist compounds having C-terminal primary amide.³⁴¹ <table border="1"> <thead> <tr> <th>Compound No.</th><th>Sequence</th></tr> </thead> <tbody> <tr><td>1</td><td>Hy-Y-Alb-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH₂</td></tr> <tr><td>2</td><td>Hy-Y-Alb-EGTFTSDYSI-Alb-LDKKAQRAFIWVLLAQGPSSGAPPPS-NH₂</td></tr> <tr><td>3</td><td>Hy-Y-Alb-EGTFTSDYSIALDKIAGRAFNWLVAlb-K-NH₂</td></tr> <tr><td>4</td><td>Hy-Y-Alb-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH₂</td></tr> <tr><td>5</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> </tbody> </table> <table border="1"> <thead> <tr> <th>Compound No.</th><th>Sequence</th></tr> </thead> <tbody> <tr><td>6</td><td>pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>7</td><td>Hy-YGEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>8</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>9</td><td>Hy-Y-Alb-EGTFTSDLSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>10</td><td>Hy-Y-Alb-EGTFTSDSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>11</td><td>Hy-Y-Alb-EGTFTSDYLIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>12</td><td>Hy-Y-Alb-EGTFTSDYSIALDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>13</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>14</td><td>Hy-Y-Alb-EGTFTSDYSIYLEKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>15</td><td>Hy-Y-Alb-EGTFTSDYSIALEKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>16</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>17</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>18</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>19</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>20</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>21</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> <tr><td>22</td><td>Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH₂</td></tr> </tbody> </table> <ul style="list-style-type: none"> Use of pharmaceutically acceptable salts of peptides. <p>“The GIP/GLP-1 dual agonist compounds of the present invention, or salts or solvates thereof, may be formulated as pharmaceutical compositions prepared for storage or administration, which typically comprise a therapeutically effective amount of a compound employed in the context of the invention, or salts or solvates thereof, in a pharmaceutically acceptable carrier.”³⁴²</p>	Compound No.	Sequence	1	Hy-Y-Alb-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂	2	Hy-Y-Alb-EGTFTSDYSI-Alb-LDKKAQRAFIWVLLAQGPSSGAPPPS-NH ₂	3	Hy-Y-Alb-EGTFTSDYSIALDKIAGRAFNWLVAlb-K-NH ₂	4	Hy-Y-Alb-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH ₂	5	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	Compound No.	Sequence	6	pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	7	Hy-YGEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	8	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	9	Hy-Y-Alb-EGTFTSDLSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	10	Hy-Y-Alb-EGTFTSDSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	11	Hy-Y-Alb-EGTFTSDYLIYLDKKAQRAFNWLLA-Alb-K-NH ₂	12	Hy-Y-Alb-EGTFTSDYSIALDKKAQRAFNWLLA-Alb-K-NH ₂	13	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	14	Hy-Y-Alb-EGTFTSDYSIYLEKKAQRAFNWLLA-Alb-K-NH ₂	15	Hy-Y-Alb-EGTFTSDYSIALEKKAQRAFNWLLA-Alb-K-NH ₂	16	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	17	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	18	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	19	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	20	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	21	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂	22	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂
Compound No.	Sequence																																																
1	Hy-Y-Alb-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂																																																
2	Hy-Y-Alb-EGTFTSDYSI-Alb-LDKKAQRAFIWVLLAQGPSSGAPPPS-NH ₂																																																
3	Hy-Y-Alb-EGTFTSDYSIALDKIAGRAFNWLVAlb-K-NH ₂																																																
4	Hy-Y-Alb-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH ₂																																																
5	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
Compound No.	Sequence																																																
6	pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
7	Hy-YGEGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
8	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
9	Hy-Y-Alb-EGTFTSDLSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
10	Hy-Y-Alb-EGTFTSDSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
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21	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																
22	Hy-Y-Alb-EGTFTSDYSIYLDKKAQRAFNWLLA-Alb-K-NH ₂																																																

	<p>“The term "pharmaceutically acceptable salt" refers to a salt of the compound. Salts include pharmaceutically acceptable salts, such as, e.g., acid addition salts and basic salts. Examples of acid addition salts include hydrochloride salts, citrate salts and acetate salts.”³⁴³</p>
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167. Accordingly, the combined teachings of the '657, '483, and '537 Publications teach or suggest each element of claim 1 and the compound of claim 1 as a whole.

B. Claim 2

2. The compound of claim 1, wherein X₃ is Phe.

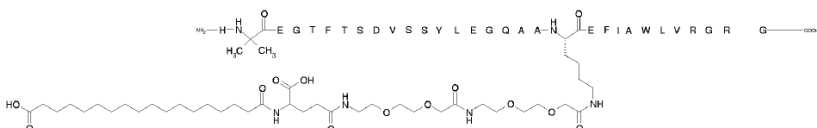
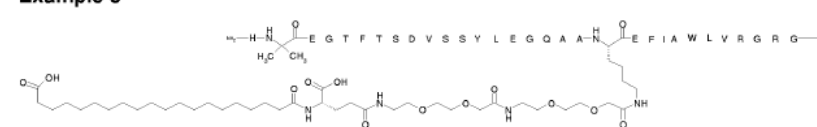
168. Claim 2 is obvious for the same reasons discussed above for claim 1. Among other things, both the '657 and '483 Publications disclose Phe²², consistent with excellent GIP/GLP-1 receptor dual agonism. Accordingly, claim 2 as a whole was obvious.

³⁴⁰ EX1007, 2:23.

³⁴¹ EX1008, 65-67 (Tables 1-2).

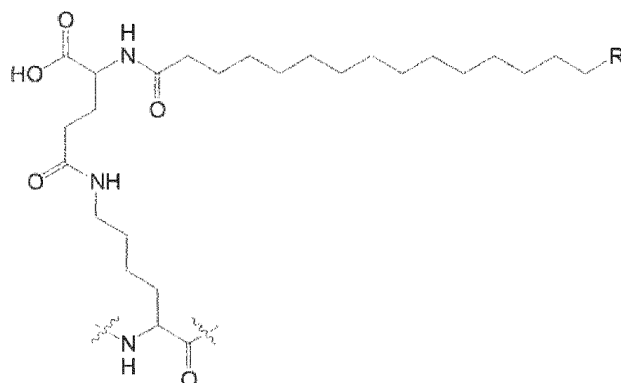
³⁴² EX1008, [0081].

³⁴³ EX1008, [0084].

Claim 4	Prior Art
<p>b is 14 to 18</p>	<p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> • b is 16 or 18 <p>Example 4</p> <p>5 N-ε²⁶-[2-(2-[2-(2-[2-(4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p>  <p>[Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide</p> <p>10 synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was</p> <p>Example 5</p>  <p>25 N-ε²⁶-[2-(2-[2-(2-[2-(4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> • b is 14 to 18. <p>“The lipophilic substituent may include a hydrocarbon chain having 10 to 24 carbon (C) atoms....Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³⁴⁶</p> <p>“An example of a lipophilic substituent comprising a lipophilic</p>

³⁴⁶ EX1008, [0061].

moiety Z^1 and spacer Z^2 is shown in the formula below.³⁴⁷



E. Claim 5

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

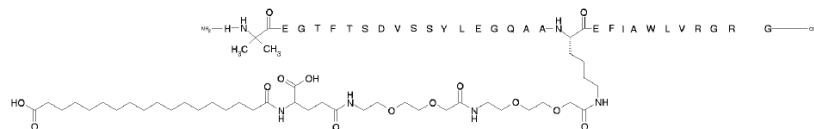
171. Claim 5 is obvious for the same reasons discussed above for claims 1, 2 and 4. Among other things, the '537 Publication Examples 4-5 disclose b is 16 and 18 respectively, satisfying the limitation “wherein b is 16 to 18.” This is supported by the disclosure of the '483 Publication. EX1008, [0061], [0065]. Accordingly, claim 5 as a whole was obvious.

Claim 5	Prior Art
b is 16 to 18	<p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> b is 16 or 18

³⁴⁷ EX1008, [0065].

Example 4

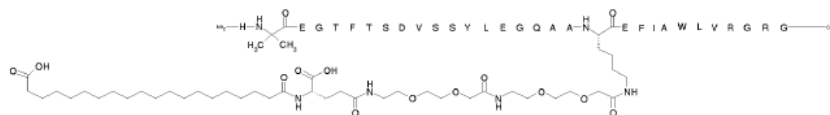
- 5 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



- 10 [Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide 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]acetyl)amino]ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.



The '483 Publication teaches:

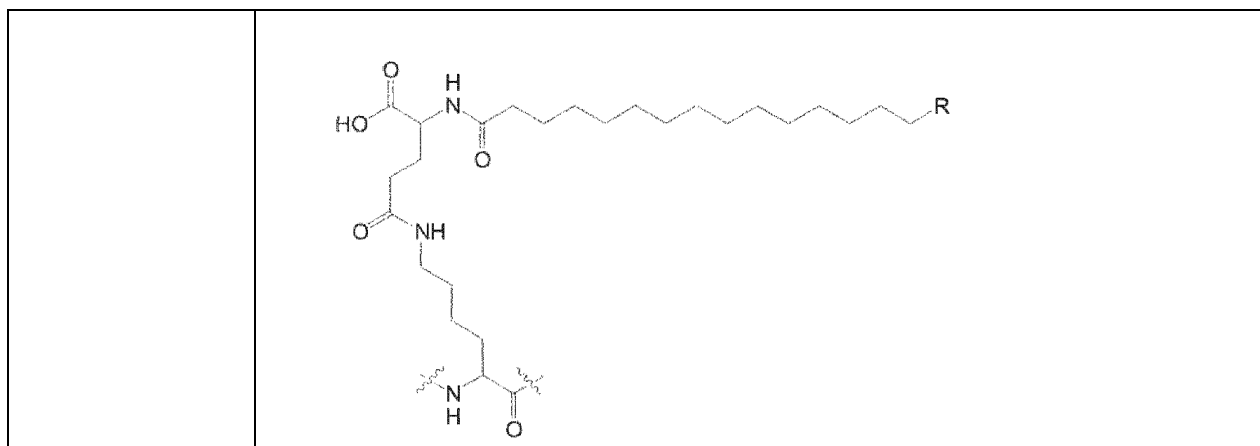
- b is 16 to 18.

“The lipophilic substituent may include a **hydrocarbon chain having 10 to 24 carbon (C) atoms**....Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³⁴⁸

“An example of a lipophilic substituent comprising a lipophilic moiety Z¹ and spacer Z² is shown in the formula below.”³⁴⁹

³⁴⁸ EX1008, [0061].

³⁴⁹ EX1008, [0065].

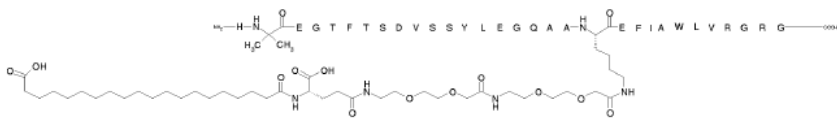


F. Claim 6

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

172. Claim 6 is obvious for the same reasons discussed above for claims 1, 2, 4-5. Among other things, the '537 Publication Example 5 discloses b is 18, satisfying the limitation “wherein b is 18.” This is supported by the disclosure of the '483 Publication. EX1008, [0061], [0065]. Accordingly, claim 6 as a whole was obvious.

Claim 5	Prior Art
b is 18	<p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> • b is 18

	<p>Example 5</p>  <p>25</p> <p>N-ε²⁶-[2-(2-[2-(2-[2-(4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> • b is 18. <p>“The lipophilic substituent may include a hydrocarbon chain having 10 to 24 carbon (C) atoms....Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³⁵⁰</p>
--	---

G. Claim 7

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

173. Claim 7 is obvious for the same reasons discussed above for claims 1, 2, and 4. Among other things, the '537 Publication Examples 4 and 5 disclose a is 1, satisfying the limitation “wherein a is 1.” This is supported by the disclosure of the '483 Publication. EX1008, [0065]-[0066]. Accordingly, claim 7 as a whole was obvious.

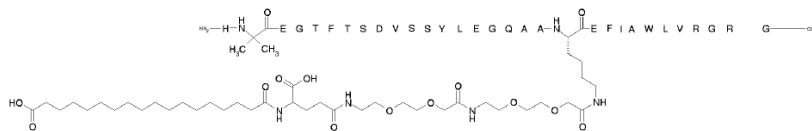
Claim 7	Prior Art
a is 1	The '537 Publication teaches:

³⁵⁰ EX1008, [0061].

- a is 1

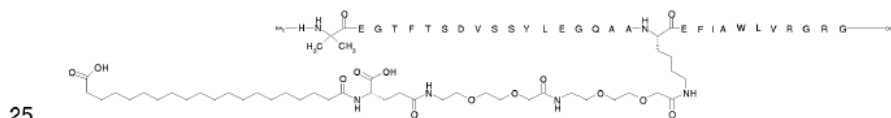
Example 4

5 N-ε²⁶-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-
carboxybutyrylamino]ethoxy)ethoxy]acetyl)amino]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

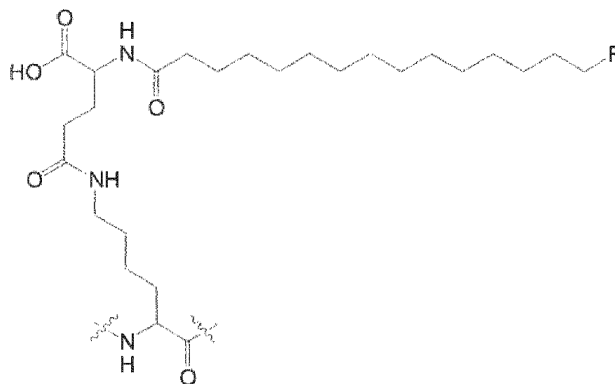


N-ε²⁶-[2-(2-[2-(2-[2-(4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino)ethoxy]ethoxy]acetyl)amino)ethoxy]ethoxy]acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

The '483 Publication teaches:

- a is 1.

“An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:



“Here, the side chain of a Lys residue is covalently attached to a

	γ Glu spacer (Z^2) via an amide linkage.” ³⁵¹
--	--

H. Claim 9

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

174. Claim 9 is obvious for the same reasons discussed above for claims 1, 2, and 4. Among other things, both the '657 and '483 Publications disclose the C-terminal amino acid is amidated as a C-terminal primary amide.³⁵² Accordingly, claim 9 as a whole was obvious.

³⁵¹ EX1008, [0065]-[0066].

³⁵² EX1007, 2:23-31 (“the C-terminal amino acid is optionally amidated”); EX1008, 65-67 (Tables 1-2 showing compounds with C-terminal primary amide).

Claim 9	Prior Art																																																
C-terminal primary amide	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none">The C-terminal amino acid is optionally amidated. <p>“[T]he C-terminal amino acid is optionally amidated[.]”³⁵³</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none">GIP/GLP-1 receptor dual agonist compounds having C-terminal primary amide.³⁵⁴ <div><p>Table 1.</p><table><tr><th>Compound No.</th><th>Sequence</th></tr><tr><td>1</td><td>Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH₂</td></tr><tr><td>2</td><td>Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFEVWLLAQGPSGAPPPS-NH₂</td></tr><tr><td>3</td><td>Hy-Y-Aib-EGTFTSDYSIALDKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>4</td><td>Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH₂</td></tr><tr><td>5</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr></table><p>Table 2.</p><table><tr><th>Compound No.</th><th>Sequence</th></tr><tr><td>6</td><td>pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>7</td><td>Hy-Y-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>8</td><td>Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>9</td><td>Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>10</td><td>Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>11</td><td>Hy-Y-Aib-EGTFTSDYLYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>12</td><td>Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>13</td><td>Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>14</td><td>Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>15</td><td>Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>16</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>17</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>18</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>19</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH₂</td></tr><tr><td>20</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>21</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr><tr><td>22</td><td>Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH₂</td></tr></table></div> <p>65</p>	Compound No.	Sequence	1	Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂	2	Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFEVWLLAQGPSGAPPPS-NH ₂	3	Hy-Y-Aib-EGTFTSDYSIALDKAQRAFNWLLA-Aib-K-NH ₂	4	Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂	5	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	Compound No.	Sequence	6	pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	7	Hy-Y-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	8	Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	9	Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	10	Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	11	Hy-Y-Aib-EGTFTSDYLYLDKKAQRAFNWLLA-Aib-K-NH ₂	12	Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFNWLLA-Aib-K-NH ₂	13	Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFNWLLA-Aib-K-NH ₂	14	Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFNWLLA-Aib-K-NH ₂	15	Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFNWLLA-Aib-K-NH ₂	16	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	17	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	18	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	19	Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH ₂	20	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	21	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂	22	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂
	Compound No.	Sequence																																															
	1	Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂																																															
	2	Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFEVWLLAQGPSGAPPPS-NH ₂																																															
	3	Hy-Y-Aib-EGTFTSDYSIALDKAQRAFNWLLA-Aib-K-NH ₂																																															
4	Hy-Y-Aib-EGTFISDYSIYLEKKAKEFVNWLLAQK-NH ₂																																																
5	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
Compound No.	Sequence																																																
6	pGlu-YAEGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
7	Hy-Y-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
8	Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
9	Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
10	Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
11	Hy-Y-Aib-EGTFTSDYLYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
12	Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFNWLLA-Aib-K-NH ₂																																																
13	Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFNWLLA-Aib-K-NH ₂																																																
14	Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFNWLLA-Aib-K-NH ₂																																																
15	Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFNWLLA-Aib-K-NH ₂																																																
16	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
17	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
18	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
19	Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH ₂																																																
20	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
21	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
22	Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFNWLLA-Aib-K-NH ₂																																																
	<ul style="list-style-type: none">Use of pharmaceutically acceptable salts of peptides. <p>“The GIP/GLP-1 dual agonist compounds of the present invention, or salts or solvates thereof, may be formulated as pharmaceutical compositions prepared for storage or administration, which typically comprise a therapeutically effective amount of a compound employed in the context of the invention, or salts or solvates thereof, in a pharmaceutically acceptable carrier. ”³⁵⁵</p>																																																

	<p>“The term ‘pharmaceutically acceptable salt’ refers to a salt of the compound. Salts include pharmaceutically acceptable salts, such as, e.g., acid addition salts and basic salts. Examples of acid addition salts include hydrochloride salts, citrate salts and acetate salts.”³⁵⁶</p>
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I. Claim 10

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 sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γ -Glu)₁-CO-(CH₂)₁₈-CO₂H;

X₃ is Phe;

and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 3) or a pharmaceutically acceptable salt thereof.

175. Claim 10 is obvious for the same reasons discussed above for claims 1-7 and 9. Among other things, both the '657 and '483 Publications disclose Phe²², consistent with excellent GIP/GLP-1 receptor dual agonism. Furthermore, the '537 Publication Examples 4-5 disclose b is 16 and 18 respectively, satisfying the

³⁵³ EX1007, 2:23.

³⁵⁴ EX1008, 65-67 (Tables 1-2).

³⁵⁵ EX1008, [0081].

³⁵⁶ EX1008, [0084].

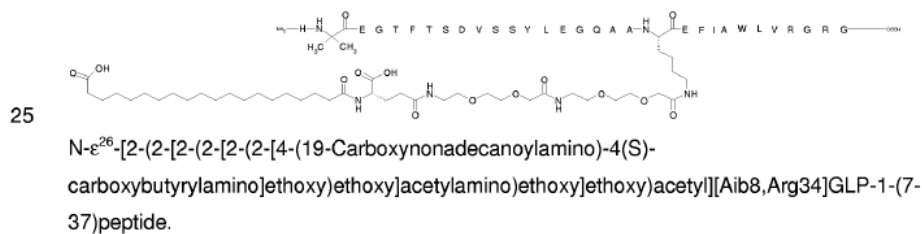
limitation b is 18. Additionally, the '537 Publication Examples 4-5 disclose a is 1.

Accordingly, claim 10 as a whole was obvious.

Claim 10	Prior Art
<p>Claim 1, wherein</p> <p>X₃ is Phe</p> <p>A is 1</p> <p>B is 18</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> • Phe^{22,357} <p>The present invention provides a peptide comprising the sequence:</p> <pre> 15 Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- 5 10 Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa¹-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 Xaa²-Xaa³ (SEQ ID NO:1) 20 25 </pre> <p>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.</p> <p>The '537 Publication teaches:</p> <ul style="list-style-type: none"> • The claimed albumin-binding moiety conjugated to epsilon-amino group of Lys²⁰.

³⁵⁷ EX1007, 2:12-25 (claimed sequence residues highlighted in green).

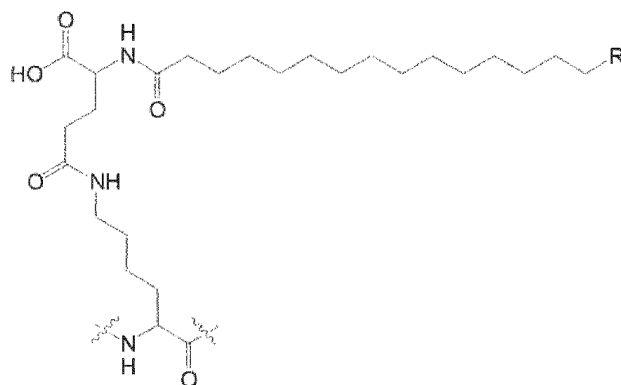
Example 5



The '483 Publication teaches:

- a is 1.

“An example of a lipophilic substituent comprising a lipophilic moiety Z¹ and spacer Z² is shown in the formula below:



“Here, the side chain of a Lys residue is covalently attached to a **γGlu spacer (Z²)** via an amide linkage.”³⁵⁸

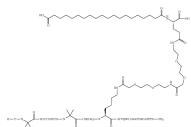
- b is 18.

“The lipophilic substituent may include **a hydrocarbon chain having 10 to 24 carbon (C) atoms**....Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³⁵⁹

³⁵⁸ EX1008, [0065]-[0066].

³⁵⁹ EX1008, [0061].

176. Claim 15 visually depicts the claimed peptide wherein the peptide sequence (P) has a Phe (F) at position 22 and wherein the albumin-binding moiety (M) has 18 methylene units (b=18) and one γ Glu (a=1). Claim 15 is obvious for the same reasons discussed above for claims 1-7 and 9-10. Among other things, both the '657 and '483 Publications disclose Phe²², consistent with excellent GIP/GLP-1 receptor dual agonism. Furthermore, the '537 Publication Examples 4-5 disclose b is 16 and 18 respectively, satisfying the limitation b is 18. Additionally, the '537 Publication Examples 4-5 disclose a is 1. Accordingly, claim 15 as a whole was obvious.

Claim 15	Prior Art
	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> • Phe^{22,361}

³⁶¹ EX1007, 2:12-25 (claimed sequence residues highlighted in green).

The present invention provides a peptide comprising the sequence:

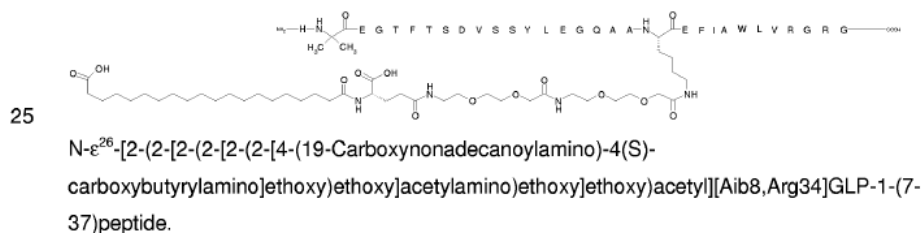
15 Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
5 10
15 Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa¹-Val-Gln-Trp-Leu-Ile-Ala-
20 25
Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln-
30 35 40
20 Xaa²-Xaa³ (SEQ ID NO:1)

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
25 both are optionally PEGylated.

The '537 Publication teaches:

- The claimed albumin-binding moiety conjugated to epsilon-amino group of Lys²⁰.

Example 5

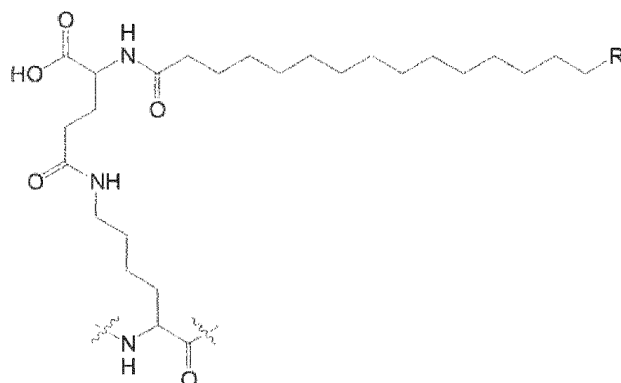


The '483 Publication teaches:

- a is 1.

“An example of a lipophilic substituent comprising a lipophilic

moiety Z^1 and spacer Z^2 is shown in the formula below:



“Here, the side chain of a Lys residue is covalently attached to a γ **Glu spacer** (Z^2) via an amide linkage.”³⁶²

- b is 18.

“The lipophilic substituent may include a **hydrocarbon chain having 10 to 24 carbon (C) atoms**....Preferably it has at least 11 atoms, and preferably it has 18 C atoms or fewer.”³⁶³

K. Claims 12 and 16

12 [16]. A pharmaceutical composition comprising the compound of claim 10 [15] with a pharmaceutically acceptable carrier, diluent, or excipient.

177. Claims 12 and 16 are each obvious for the same reasons discussed above for claims 1-7, 9-10, and 15. Among other things, both the '657 and '483 Publications disclose a pharmaceutical composition comprising the compound with a pharmaceutically acceptable carrier, diluent, or excipient.

³⁶² EX1008, [0065]-[0066].

³⁶³ EX1008, [0061].

178. For example, the '657 Publication teaches formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient, including together with other therapeutic agents.³⁶⁴ It teaches that the peptides are preferably formulated as pharmaceutical compositions administered by a variety of routes, and that such formulations and processes for preparing the same are well known in the art.³⁶⁵

179. As further example, the '483 Publication teaches formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient, including for administration by injection.³⁶⁶ It teaches that formulations and processes for preparing the same are well known in the art.³⁶⁷

180. Accordingly, each of claims 12 and 16 as a whole was obvious.

³⁶⁴ EX1007, 4:26-5:21, Claims 13-14.

³⁶⁵ EX1007, 25:4-9.

³⁶⁶ EX1008, [0081], Claims 25-27.

³⁶⁷ EX1008, [0083]-[0084], [0086].

Claims 12/16	Prior Art
<p>A pharmaceutical composition comprising the compound of claim 10 [15] with a pharmaceutically acceptable carrier, diluent, or excipient.</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> Formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient <p>“This invention also provides the use of a peptide of the invention for the manufacture of a medicament for the treatment of diabetes mellitus...[or] obesity....Additionally, this invention provides a pharmaceutical formulation comprising a peptide of the invention with a pharmaceutically acceptable carrier, diluent, or excipient.”³⁶⁸</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> Formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient. <p>“The GIP/GLP-1 dual agonist compounds of the present invention, or salts or solvates thereof, may be formulated as pharmaceutical compositions prepared for storage or administration,...in a pharmaceutically acceptable carrier. In some embodiments, the pharmaceutical composition is formulated as a liquid suitable for administration by injection or infusion, or which is formulated to cause slow release of the GIP/GLP-1 dual agonist compound.”³⁶⁹</p>

³⁶⁸ EX1007, 4:26-5:21; *see also* EX1007, Claim 13.

³⁶⁹ EX1008, [0081]; *see also* Claims 25-27.

L. Claims 13 and 17

13 [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 10 [15].

181. Claims 13 and 17 are each obvious for the same reasons discussed above for claims 1-7, 10 and 15. Among other things, both the '657 and '483 Publications disclose a method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a GIP/GLP-1 receptor dual agonist peptide.

182. For example, the '657 Publication teaches treating diabetes and/or obesity by administering to a patient in need thereof an effective amount of a peptide of the invention.³⁷⁰ 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.”³⁷¹

183. In further example, the '483 Publication teaches use of dual GIP/GLP-1 agonists for the treatment of metabolic disease such as diabetes and obesity, including by reducing blood glucose, inducing weight and fat loss, and by reducing high cholesterol.³⁷²

³⁷⁰ EX1007, 3:32-4:14 (“method for inducing weight loss”), Claims 15-19.

³⁷¹ EX1007, 25:9-20.

³⁷² EX1008, [0052], [0071], [0077]-[0078], [0085], Claims 28-36, 45-49.

184. Accordingly, each of claims 13 and 17 as a whole was obvious.

Claims 13/17	Prior Art
<p>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 [15].</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> • A method of treating diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a GIP/GLP-1 receptor dual agonist compound. <p>“The present invention also provides a method for treating diabetes mellitus in a patient by administering to a patient in need of such treatment an effective amount of a peptide of the invention....a method for treating insulin-dependent diabetes mellitus....”³⁷³</p> <p>“A method for treating diabetes mellitus in a patient by administering to the patient an effective amount of a peptide of any of Claims 1 to 12.”³⁷⁴</p> <p>“The compounds of the present invention are generally effective over a wide dosage range. For example, dosages per week fall within the range of 1 to 24 mg of peptide conjugate or 0.014 to 0.343 mg/kg of body weight.”³⁷⁵</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> • A method of treating type 2 diabetes mellitus, comprising administering to a patient in need thereof, an effective amount of a GIP/GLP-1 receptor dual agonist compound. <p>“A method of treatment and/or prevention of a diabetes related disorder in a patient in need thereof comprising the step of administering to said patient an effective amount of the GIP analogue of any one of claims 1 to 23....wherein the diabetes related disorder is selected from...type 2 diabetes....”³⁷⁶</p> <p>“The GIP analogue compounds employed in the context of the invention may provide an attractive treatment option for</p>

	<p>metabolic diseases including obesity, diabetes mellitus (diabetes), obesity-related disorders, and diabetes-related disorders.”³⁷⁷</p> <p>“The GIP/GLP-1 dual agonist compounds employed in the context of the invention may also be used for treatment of insulin resistance, glucose intolerance, pre-diabetes, increased fasting glucose, type 2 diabetes, hypertension, dyslipidemia (or a combination of these metabolic risk factors), atherosclerosis, arteriosclerosis, coronary heart disease, peripheral artery disease and stroke.”³⁷⁸</p>
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M. Claims 14 and 18

14 [18]. The method of claim 13 [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.

185. Claims 14 and 18 are each obvious for the same reasons discussed above for claims 1-7, 10 and 15, 13 and 17. Among other things, the ’657 Publication teaches formulating the peptide in a pharmaceutical formulation together with “other therapeutic agents.”³⁷⁹ Additionally, the ’483 Publication

³⁷³ EX1007, 3:32-4:6.

³⁷⁴ EX1007, Claim 15.

³⁷⁵ EX1007, 25:10-12.

³⁷⁶ EX1008, Claims 48-49.

³⁷⁷ EX1008, [0071].

³⁷⁸ EX1008, [0078]; *see also* EX1008, [0052], [0077], [0085], Claims 29, 31, 46-47.

³⁷⁹ EX1007, 4:26-5:21, Claim 14.

specifically teaches administration in combination therapy, including in combination with **metformin**, **sulfonylurea**, a glinide, a **DPP-IV inhibitor**, a glitazone, or insulin, and other actives.³⁸⁰ Accordingly, each of claims 14 and 18 as a whole was obvious.

Claims 14/18	Prior Art
<p>14 [18]. The method of claim 13 [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.</p>	<p>The '657 Publication teaches:</p> <ul style="list-style-type: none"> • Co-administration with other therapeutic agents. <p>“In a particular embodiment, the composition further comprises one or more other therapeutic agents.”³⁸¹</p> <p>The '483 Publication teaches:</p> <ul style="list-style-type: none"> • Co-administration with an effective amount of metformin, sulfonylurea, or DPP-IV inhibitor. <p>“In certain embodiments, a GIP/GLP-1 dual agonist compound employed in the context of the invention may be administered as part of a combination therapy with at least one other agent for treatment of diabetes...including but not limited to metformin, a sulfonylurea, a glinide, a DPP-IV inhibitor, a glitazone, or insulin. In certain embodiments, the compound or salt or solvate thereof is used in combination with insulin, DPP-IV inhibitor, sulfonylurea or metformin, particularly sulfonylurea or metformin, for achieving adequate glycemic control.”³⁸²</p>

³⁸⁰ EX1008, [0087]-[0090].

³⁸¹ EX1007, 5:20-21; *see also* Claim 14.

³⁸² EX1008, [0087]-[0088].

X. SECONDARY CONSIDERATIONS

186. I am informed that determining obviousness entails evaluating secondary considerations for indicia salient to 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 result are salient to obviousness when they represent a difference in kind rather than degree as compared to the closest prior art.

187. 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.³⁸³

188. I also have reviewed the '780 patent in its entirety to try to identify any secondary considerations of non-obviousness. I did not find any secondary considerations indicative of non-obviousness in the '780 patent.

189. I considered the patent's assertions of unmet need. The patent admits that mono-agonists of each of GIP and GLP-1 were known, but asserts that a "compound for T2D is needed that utilizes a dual mechanism of action" to achieve better efficacy than either pathway alone, and to reduce adverse effects that result

³⁸³ See Section IV.C above.

when using GLP-1 receptor agonists alone at high doses.³⁸⁴ Additionally, the patent asserts that synthetic peptide versions were needed for therapeutic application with reduced susceptibility to proteolytic degradation (e.g., DPP-IV-catalyzed inactivation) as compared to the natural ligands.³⁸⁵ Although I agree that those in the field were motivated to make and develop synthetic GIP/GLP-1 receptor dual agonists because of their known promise to treat type-2 diabetes and diabetes, and understood quite well that synthetic versions would be made more proteolytically stable than the endogenous ligands, there was no **unmet** need for any of these things. As explained throughout my declaration above, it was well-within the technical ability of a POSA to achieve each of these aims as they were amply addressed by the prior art.

190. From the perspective of a POSA, there was no unmet need evidencing non-obviousness of the claimed peptides, certainly no long-felt, unmet need or failure of others. To the contrary, the state of the art had matured by January 9, 2015, to invite routine synthesis and testing of the obvious compounds within the scope of the challenged claims by a POSA.³⁸⁶ Prior art GIP/GLP-1 receptor dual agonist peptides demonstrated biological activity comparable to that observed

³⁸⁴ EX1001, 1:15-20, 1:36-44, 2:13-22.

³⁸⁵ EX1001, 1:41-44.

³⁸⁶ See Section VII above.

using the claimed peptides,³⁸⁷ though precise comparisons require caution due to differences in the models used to test them. With the disclosure in December 2014 that Novo Nordisk was developing the GLP-1R agonist semaglutide for once-weekly administration, the time was ripe for a POSA to make and test the obvious dual agonist compounds within the scope of the challenged claims for all the reasons I have discussed above.

191. I also evaluated the test results reported in the '780 patent.³⁸⁸ I evaluated whether they provide a comparison to the closest prior art, whether the results represent a difference in degree or kind, and whether the results were unexpected. In each case, the answer is no.

192. The test results in the patent fail to afford a comparison to the closest prior art. For example, Tables 8-14 are designed to evaluate whether the result obtained for one or more peptide with the scope of claim 1 (Examples 1-8) is statistically significantly different than Control. They do not provide any comparison to any prior art GIP/GLP-1 receptor dual agonist. Nor do they provide the direct comparison to semaglutide as they did for control, though semaglutide is

³⁸⁷ Prior art dual agonists routinely exhibited activity similar to the activity the challenged patent describes as desirably “balanced” co-agonist activity for GIP And GLP-1 receptor. EX1001, 6:36-43 (describing “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); *see also* Section VIII above.

³⁸⁸ EX1001, 8:55-28:17 & Tables 1-15.

not the closest prior art (in any event). Semaglutide is not a GIP/GLP-1 receptor dual agonist. As I explained above, the prior art disclosed effective GIP/GLP-1 receptor dual agonists. None of the activity assays in the '780 patent provide any comparison to any prior art GIP/GLP-1 receptor dual agonist, much less to the closest prior art. There is no demonstration of any difference in kind as compared to the closest prior art in any of Tables 1-15.

193. Nor do the test results in the '780 patent demonstrate any difference in kind between the claimed peptides that were tested. For example, Tables 11-13 report that the tested Example peptides all significantly and similarly reduced blood glucose, plasma cholesterol, and triglycerides as compared to controls.³⁸⁹ All of the GIP/GLP-1 receptor dual agonist peptides tested reduced body weight and fat mass as compared to control, and generally to the same degree. Tables 8-10. All of them bind the human GIP and GLP-1 receptors with high affinity, activate them with nanomolar potency, are selective against GLP-2 receptor, and stimulate insulin secretion (Tables 1-5 & 7).³⁹⁰ Though the tables, if accepted, indicate that the tested Example peptides all worked, and suggest that they worked generally

³⁸⁹ The patent does not explain why it failed to report the data for Example peptide 4.

³⁹⁰ All of these effects are exactly what was expected from GIP/GLP-1 receptor dual agonists, as I explained at length above.

similarly to one another, they do not support a conclusion that any of them is clearly superior over the others.³⁹¹

194. Table 6 also does not demonstrate any difference in kind as compared to the closest prior art. It provides no comparison to any prior art GIP/GLP-1 receptor dual agonist, much less to the closest prior art. I explained at length above that it was not unexpected to achieve once-weekly dosing using the prior art albumin-binding moiety that is claimed by the '780 patent here. Table 6 reported certain mean pharmacokinetic parameters for certain of the Example peptides, all within the scope of claim 1. In each case, the sample size (n) is only 2. Because the sample size is so small, a POSA would not conclude that the reported mean values in half-life represent a truly discernable difference, as opposed to observation of error.

195. To the extent the patent argues using exenatide's C-terminal motif improves the immunogenicity profile of the peptide³⁹², this was not an unexpected result, as discussed at length above.³⁹³

196. Accordingly, none of the data in the challenged patent demonstrates any unexpected result, much less any difference in kind, as compared to the closest

³⁹¹ See also Section IV.B above.

³⁹² EX1001, 20:45-21:7

³⁹³ See Section IV above.

prior art.

XI. CONCLUDING STATEMENTS

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

198. 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: May 21, 2025

By:  _____

Virginia W. Cornish, Ph.D.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42	GLP	GLP-1
GLP	Y	A	E	G	T	F	L	S	D	V	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q			
GLP-1	H	A	E	G	T	F	L	S	D	V	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q			
Utriglutide	H	A	E	G	T	F	L	S	D	V	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q			
Exenatide	H	A	E	G	T	F	L	S	D	V	S	I	A	M	D	K	I	H	Q	Q	D	F	V	N	W	L	A	Q	K	G	K	K	N	D	W	K	H	N	I	T	Q			
Compound 2	Y	Alb	E	G	T	F	L	S	D	V	S	I	Alb	L	D	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 55	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 39	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 39	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 43	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 37	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 36	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 40	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 32	Y	Alb	E	G	T	F	L	S	D	V	S	I	Alb	L	D	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 41	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 3	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	I	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2													
Compound 19	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 19	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 44	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	NH2														
Compound 17	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	S	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2													
Compound 31	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 29	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 35	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 5	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 33	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 14	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 54	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	N	W	L	L	A	Q	K	NH2														
Compound 34	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 20	Y	Alb	E	G	T	F	L	S	D	V	S	I	Y	L	D	K	A	Q	R	A	F	V	K	W	L	L	A	Q	K	NH2														
																																</												

Green = conserved across peptides

Light Blue = GLP

Dark Blue = GLP-1

Light Purple = Exenatide

XII. APPENDIX I

TABLE A

TABLE B

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	
GP	Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	A	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	N	D	W	K	H	N	I	
GP-1	H	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	A	Q	Q	D	F	V	N	W	L	L	A	Q	K	G	K	N	D	W	K	H	N	I	
Ultratide	H	A	E	G	T	F	T	S	D	Y	S	S	I	V	E	G	Q	A	A	K ⁺⁺	E	F	I	A	W	L	V	K	G	R	G	NH2									
Exenatide	H	A	E	G	T	F	T	S	D	L	S	S	K	Q	M	E	E	A	V	R	L	F	I	E	W	L	K	N	G	R	G	P	S	S	G	A	P	P	S	NH2	
Compound 28	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	G	P	S	S	G	A	P	P	S	NH2	
Compound 19	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	Q	K	E	F	V	N	W	L	L	A	Aib	K	NH2									
Compound 17	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2									
Compound 24	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2									
Compound 55	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	S	NH2	
Compound 14	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2									
Compound 29	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	G	P	S	S	G	A	P	P	S	NH2	
Compound 30	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	E	K	K	A	A	K	E	F	V	N	W	L	L	A	A	Q	K	NH2								
Compound 39	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	E	K	K	A	A	Q	K	E	F	V	E	W	L	L	S	A	NH2									
Compound 41	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	E	S	K	A	A	H	D	F	V	N	W	L	L	S	A	NH2										
Compound 16	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	S	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2									
Compound 23	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	S	K	A	Q	R	A	F	V	N	W	L	L	K	A	Aib	K	NH2								
Compound 42	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	K	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2										
Compound 44	Y	Aib	E	G	T	F	T	S	D	Y	S	I	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	Aib	K	NH2								
Compound 9	Y	Aib	E	G	T	F	T	S	D	L	S	S	I	Y	L	D	S	K	A	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2								
Compound 2	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	S	NH2		
Compound 36	Y	Aib	E	G	T	F	T	S	D	Y	S	I	A	L	D	S	K	A	K	R	A	F	V	N	W	L	L	V	A	Aib	K	P	S	S	G	A	P	P	S	NH2	
Compound 18	Y	Aib	E	G	T	F	T	S	D	Y	S	I	A	L	D	S	K	A	K	R	A	F	V	N	W	L	L	V	A	Aib	K	P	S	S	G	A	P	P	S	NH2	
Compound 43	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	E	W	L	L	S	A	NH2											
Compound 37	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2											
Compound 32	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Aib	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	S	NH2		
Compound 38	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2											
Compound 40	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2											
Compound 3	Y	Aib	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	I	A	Q	R	A	F	V	N	W	L	L	V	A	Aib	K	NH2									
Compound 35	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K ⁺⁺	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	P	S	S	G	A	P	P	S	NH2		
Compound 5	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2										
Compound 7	Y	G	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2										
Compound 8	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2										
Compound 33	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K ⁺⁺	A	Q	R	A	F	V	E	W	L	L	A	A	Q	G	P	S	S	G	A	P	P	S	NH2	
Compound 34	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K ⁺⁺	A	Q	R	A	F	V	E	W	L	L	E	S	A	NH2										
Compound 13	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	S	D	K	A	A	Q	R	A	F	V	N	W	L	L	L	A	Aib	K	NH2									
Compound 54	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K ⁺⁺	A	A	K	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	S	NH2		
Compound 48	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	K ⁺⁺	A	A	K	D	F	V	E	W	L	L	E	S	A	NH2									
Compound 25	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	Y	G	NH	L	D	F	NH2			
Compound 46	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	Q	R	A	F	V	E	W	L	L	S	A	NH2										
Compound 49	Y	Aib	E	G	T	F	T	S	D	Y	S	K	Y	L	D	E	K	K ⁺⁺	A	A	K	D	F	V	E	W	L	E	S	A	NH2										

TABLE C

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25	26	27	28	29	30	31	32	33	34	35	36	37	38	39	40	41	42			
WO 2011/119657	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Alb	L	D	K	I	A	Q	R	A	For	NaI	V	Q	W	L	I	A	Alb	K	K	Q	K	N	D	W	Q	I	H	N	I	Q		
gip	Y	A	E	G	T	F	I	S	D	Y	S	I	A	M	D	K	I	H	Q	R	A	F	N	W	L	L	A	Q	K	G	K	Q	K	H	Q	I	T	Q	Cor	N/A	Cor	N/A			
GLP-1	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R	G	NH2													
Ureaglutide	H	A	E	G	T	F	T	S	D	V	S	S	Y	L	E	G	Q	A	A	K	E	F	I	A	W	L	V	K	G	R	G	NH2													
Exenatide	H	G	E	G	T	F	T	S	D	L	S	K	Q	M	E	E	E	A	V	R	L	F	I	E	W	L	K	N	G	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 2	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Alb	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 55	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	S	A	G	P	S	S	G	A	P	P	P	S	NH2					
Compound 39	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	K	E	F	V	E	W	L	L	S	A	NH2															
Compound 43	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2															
Compound 37	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2															
Compound 36	Y	Alb	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	K	A	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2				
Compound 40	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	A	K	D	F	V	E	W	L	L	S	A	NH2															
Compound 32	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Alb	L	D	K	K	A	A	Q	R	A	F	V	E	W	L	L	A	Q	G	P	S	S	G	A	P	P	P	S	NH2				
Compound 41	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	D	F	V	E	W	L	L	S	A	NH2															
Compound 3	Y	Alb	E	G	T	F	T	S	D	Y	S	I	A	L	D	K	I	A	Q	R	A	F	V	N	W	L	V	A	Alb	K	NH2														
Compound 19	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	K	E	F	V	N	W	L	L	A	Alb	K	NH2														
Compound 44	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	D	F	V	E	W	L	L	R	A	NH2															
Compound 17	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2														
Compound 31	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	NH2														
Compound 29	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2					
Compound 35	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2					
Compound 5	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2					
Compound 33	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	E	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2					
Compound 14	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	R	A	F	V	N	W	L	L	A	Alb	K	P	S	S	G	A	P	P	P	S	NH2					
Compound 54	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	A	K	E	F	V	E	W	L	L	E	S	A	NH2														
Compound 34	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K	K	A	A	K	E	F	V	E	W	L	L	E	S	A	G	P	S	S	G	A	P	P	P	S	NH2			
Compound 20	Y	Alb	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	K	W	L	L	A	Alb	K	NH2														

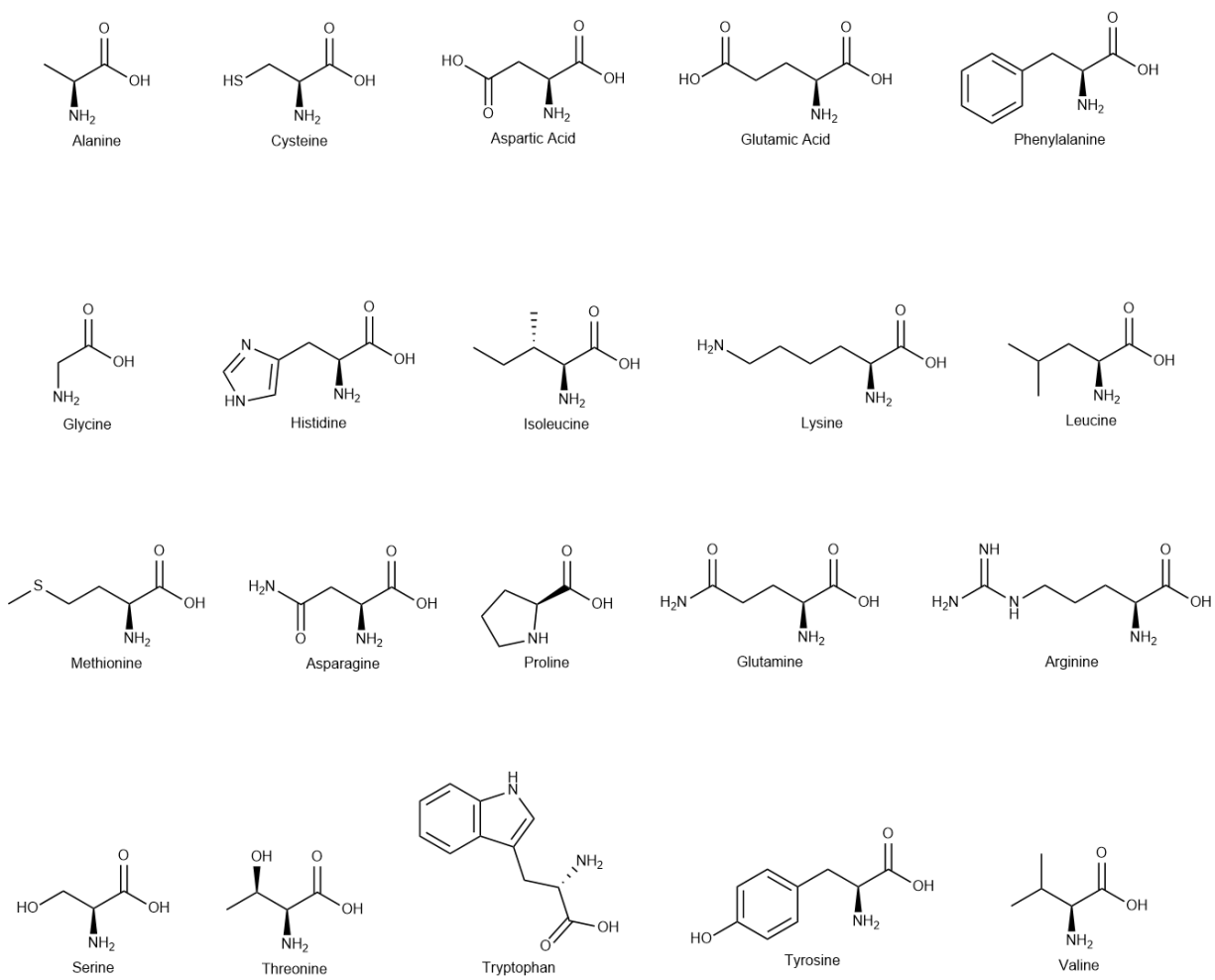
Green = conserved across peptides

Light Blue = GLP

Dark Blue = GLP-1

Light Purple = Exenatide

FIGURE 17.



XIII. APPENDIX II

Exhibit No	Description
1001	U.S. Patent No. 9,474,780.
1002	<i>Intentionally left blank</i>
1003	<i>Curriculum Vitae</i> of Dr. Virginia W. Cornish, Ph.D.
1004	Prosecution History (Excerpts) of U.S. Patent No. 9,474,780.
1005	WO 2016/111,971 Search Report.
1006	WO 2016/111,971 Written Opinion.
1007	WO 2011/119,657 A1 Publication.
1008	WO 2013/164,483 A1 Publication.
1009	WO 2006/097,537 A2 Publication.
1010	WO 2014/202,727 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”) <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf .
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1057	OZEMPIC (semaglutide) injection drug label (Dec. 2017) (“OZEMPIC”) <i>available at</i> https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/209637lbl.pdf .
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