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.

Case IPR2025-01024
US Patent No. 9,474,780

PETITION FOR INTER PARTES REVIEW

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I. INTRODUCTION

Petitioner Empower Clinic Services, L.L.C. (d/b/a Empower Pharmacy) ("Empower") requests *inter partes* review ("IPR") to cancel claims 1-7, 9-10, and 12-18 of U.S. Patent No. 9,474,780 (EX1001). As this petition shows, these claims are unpatentable.

Patentee ("Lilly") claims a peptide that is an obvious variant of a prior art peptide sharing the same utility (GIP/GLP-1 receptor dual agonism). Lilly seeks to extend its patent exclusivity years beyond the expiration date of its original patent, which covered a peptide sequence known to impart significant GIP/GLP-1 receptor dual agonism. The prior art specifically taught two straightforward ways to improve such peptides: (1) employing a common C-terminal motif derived from a natural agonist to improve *in vivo* stability in combination with excellent potency and low immunogenicity; and (2) conjugating a known albumin-binding moiety to a lysine amino acid residue at position 20 of the peptide to prolong its duration of action. Building on extensive teachings providing structure-activity-relationships for the very receptors at issue, the prior art successfully applied these techniques to improve GIP and GLP-1 receptor agonists. These successes were published by the end of 2014, before Lilly's January 2015 earliest-claimed priority date. By that time, making the claimed peptide was a simple matter of routine synthesis of a structurally-similar analogue expected to share known utility. In view of the prior

art and level of ordinary skill, a person of ordinary skill in the art ("POSA") had good reason with reasonable expectation of success for making what is claimed. Accordingly, the claims should be found obvious and cancelled.

II. MANDATORY NOTICES

A. Real Parties-In-Interest

Petitioner Empower Clinic Services, L.LC. (d/b/a Empower Pharmacy) is the real party-in-interest.

B. Related Matters

None known

C. Identification of Counsel and Service Information

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III. STANDING CERTIFICATIONS

The challenged patent is available for IPR. Empower is not barred or estopped from requesting IPR on these grounds.

IV. CHALLENGES AND PRECISE RELIEF REQUESTED

Claims 1-7, 9-10, and 12-18 are unpatentable under 35 U.S.C. §103 on these grounds:

Ground	Claims	Obvious from the Combined Teachings of
1	1-7, 9-10, 12-18	'657,[1] '483,[2] and '537[3] Publications

V. THE CHALLENGED PATENT

The challenged patent is directed to a genus of peptide compounds having utility as GIP and GLP-1 receptor co-agonists. EX1001, cover [54], Abstract; EX1002, ¶¶23-25. The patent explains that the "present invention provides

[1] WO 2011/119657.

[2] WO 2013/164483.

[3] WO 2006/097537.

compounds that display a balanced GIP and GLP-1 activity," which it describes as having "[an] affinity for GIP receptors and GLP-1 receptors in an in vitro binding assay at a molar ratio that is close to 1:1, such as 1:1 GLP-1/GIP, 2:1 GLP-1/GIP…1:2 GLP-1/GIP…." EX1001, 6:36-43. The earliest claimed priority date is January 9, 2015. EX1001, cover [60].

A. Challenged Claims

The challenged patent has 18 claims, all of which depend directly or indirectly from claim 1. EX1001, Claims; EX1002, ¶¶30-31. Independent claim 1 defines the genus of claimed peptides using standard single letter signifiers for individual amino acid residues. The claimed peptide is chemically modified through conjugation to the epsilon-amino group of the K (lysine) side chain. In claim 1, the length of the conjugated moiety is variable (10-20 methylene units in the fatty acid and 1-2 γGlu residues in the linker. Claim 1 recites this subject matter as follows:

We claim:

1. A compound of Formula:

$YX_1EGTFTSDYSIX_2LDKIAQKAX_3VQWLIAGGPSSGAPPPS;$

wherein

X_1 is Aib;

X_2 is Aib;

K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-$(\gamma Glu)_a$-CO—$(CH_2)_b$—CO_2H wherein a is 1 to 2 and b is 10 to 20;

X_3 is Phe or 1-Nal;

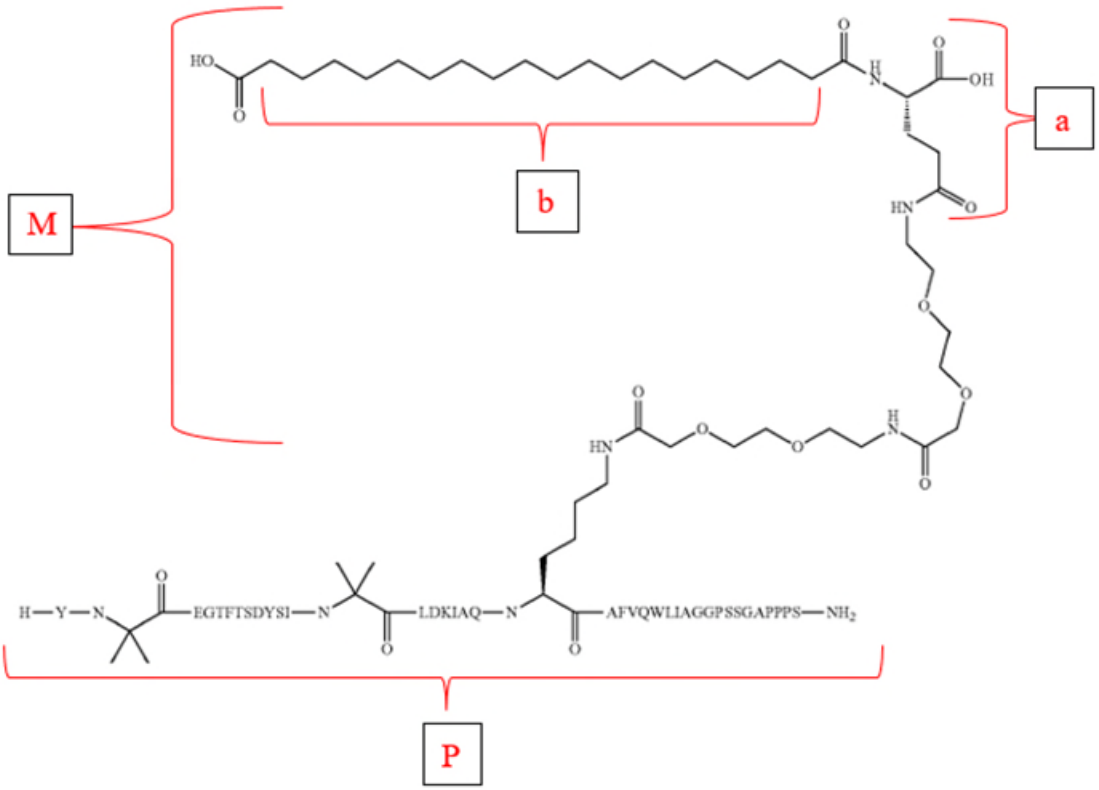
and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),

or a pharmaceutically acceptable salt thereof.

EX1001, Claim 1; EX1002, ¶26 (Aib is 2-Aminoisobutyric acid), 30, 58-59; EX1014, 119, Fig. 5-5.

As apparent from its plain language, claim 1 permits position 22 (X_3) of the peptide sequence to have either a natural Phe (F) or a synthetic 1-Nal amino acid residue, whereas dependent claims 2-3, 10-11, and 15 recite a specific one of these two options. EX1002, ¶26 (1-Nal is 1-Naphthylalanine), 31. Moreover, while claim 1 permits the conjugated moiety to expand or contract the number of methylene units in the fatty acid chain (b = 10 to 20) and the number of $_\gamma$Glu residues in the linker (a = 1 to 2), certain dependent claims (*e.g.*, 4-7) narrow one or more of these parameters.

For illustration purposes, Dr. Virginia Cornish, whose declaration (EX1002) supports this petition, has annotated the structure depicted in dependent claim 15 to identify the peptide sequence (P), the conjugated moiety (M), the methylene units (b), and the $_{\gamma}$Glu (a). EX1002, ¶176. In the case of claim 15, position 22 uses Phe rather than 1-Nal.



Other dependent claims recite formulation excipients (claims 12 & 16), a method of treating type 2 diabetes (claims 13 & 17), or combination administration with other actives (claims 14 & 18). EX1002, ¶31.

The challenged patent includes various tables comparing some or all of eight

example peptides within the scope of claim 1 to a control. EX1002, ¶¶33-40; EX1001, Table 1-15. None of these tables compare the claimed peptides to any prior art GIP/GLP-1 receptor dual agonist, much less to the closest prior art. EX1002, ¶¶33-34, 40; EX1001, 25:55-26:61, 27:40-28:17 & Tables 1-15.

B. Prosecution History

The challenged claims were allowed with minimal prosecution scrutiny. EX1002, ¶¶41-51. Indeed, they were allowed just six months after application filing. EX1004, 22; EX1002, ¶42. An earlier European search report (EX1005) and written opinion (EX1006) considered only three references. EX1002, ¶42. The U.S. examiner considered a total of thirteen publications, all identified by the applicant (none supplied by the examiner). EX1004, 36-39; EX1002, ¶43. These references did not include EX1007 or EX1009, discussed herein, among others.

The examiner discussed only one reference (EX1012), but did not identify important prior art teachings establishing the effective structure-activity relationship ("SAR") for dual GIP/GLP-1 receptor agonism. EX1004, 27-28; EX1002, ¶¶44, 47, 49. Moreover, the examiner did not identify or discuss any teaching in the prior art that Gln (Q) was an appropriate amino acid residue at position 24 for an effective dual GIP/GLP-1 receptor agonist. EX1002, ¶45. For the one reference the examiner discussed during prosecution, the examiner's belief that this reference did not teach a preference for Gln (Q) at position 24 was the

primary basis for distinguishing the reference (which the examiner concluded taught a genus of GIP/GLP-1 receptor dual agonists that otherwise encompassed the claimed amino acid sequence). EX1002, ¶¶50-51; EX1004, 28. The examiner likewise failed to identify any teaching in the prior art identifying the specific conjugated moiety recited in the claims as being used in the prior art for the very same purpose as in the challenged patent. EX1004, 27; EX1002, ¶¶48, 50. The examiner thus erroneously allowed the claims without rejection.

VI. LEVEL OF ORDINARY SKILL

The prior art discussed herein evidences knowledge and skill in the art at the time of publication before the claimed invention. As of January 9, 2015, a person of ordinary skill in the art ("POSA") would have been familiar with signaling peptides and their biochemistry, as the accompanying exhibits prove. EX1002, ¶54. A Ph.D. in chemistry, protein engineering, or a related field, or alternatively, a master's degree in one of these fields plus two to five years of experience in peptide design would represent typical education and experience for a skilled artisan. EX1002, ¶¶52-53. This individual may have worked in consultation with a team including, *e.g.*, a pharmaceutical chemist and/or a pharmacist familiar with formulating peptides for administration, and could have consulted with a physician with experience administering peptides for the treatment of diabetes or obesity. EX1002, ¶53.

Professor Virginia W. Cornish, whose declaration accompanies this petition (*see* EX1002, ¶¶8-10), has decades of experience in the relevant field. *Id.*, ¶¶1-7; EX1003. Professor Cornish was a person of ordinary skill in the art by 2015. *Id.*, ¶54.

VII. CLAIM CONSTRUCTION

The claim terms do not require construction to apply the grounds. EX1002, ¶¶55-56. Claims 1-12 and 15-16 are not limited to a specific use.

VIII. PRIOR ART

All the applied and background references were publicly available by January 9, 2015.

A. Background

Peptides are amino-acid polymers, the amino acid sequences of which are commonly specified using standardized one- or three-letter identifiers, as illustrated in the table below. EX1002, ¶¶57-60; EX1014, 118 (discussing foundations of biochemistry).

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

Glucose-dependent insulinotropic polypeptide (GIP, also called gastric inhibitory peptide) and Glucagon-like Peptide (GLP)-1 are two peptides that exist naturally in the human body. EX1002, ¶73; EX1040, 8-9 (discussing secretion and metabolism of GIP and GLP-1). Long before 2015, it was known that GIP and GLP-1 were incretins (insulin-promoting hormones) that the body releases as a signal to stop eating and to control blood sugar. EX1030, 27-28; EX1002, ¶¶73-76 (discussing EX1040-1045). Each peptide was known to operate through its own G-protein coupled receptor, though the GIP receptor (GIPR) and GLP-1 receptor (GLP-1R) were known to share significant structural and mechanistic similarities. EX1002, ¶¶68-71; EX1030, 27-28, 32. In particular, the ability of the peptide to activate the receptors depended on interactions with the N-terminal region of the peptides. EX1002, ¶72; EX1030, 28; EX1038, 419-20.

Well before 2015, researchers recognized the utility of using peptides to activate GLP-1R signaling to treating diabetes and obesity. EX1002, ¶¶79-82;

EX1030, 27-28. They also recognized that the therapeutic potential of natural GLP-1 for treating diabetes and obesity was improved by addressing (1) its short half-life (mere minutes) in the body; and (2) its rapid deactivation when DPP-IV cleaves the first two N-terminal amino acid residues from the rest of the molecule based on recognizing the Ala at position 2 (Ala^2). EX1002, ¶77; EX1030, 27-28; EX1047, 753-54; EX1048, 3587; EX1049, 21204.

In 2005, FDA approved the first GLP-1 agonist (exenatide) for the treatment of type 2 diabetes based on a natural GLP-1 agonist (exendin-4) found in Gila monster saliva. EX1053; EX1054; EX1002, ¶¶78, 80; EX1030, 28. Exenatide avoided undesirable DPP-IV cleavage by employing Gly at position 2 rather than the Ala^2 found in human GLP-1. EX1002, ¶¶78, 80; EX1030, 28; EX1053, 1, 16; EX1054, 1-2. Exenatide also was more potent than human GLP-1 and had greater non-DPP-IV-related metabolic stability, which was attributed at least in part to its C-terminal motif (GGPSSGAPPPS). EX1002, ¶¶94-96; EX1069, Abstract, 7-8, Table 1, Table 4. Exenatide was sold in twice-daily and once-weekly formulations as Byetta™ and Bydureon™. EX1002, ¶111; EX1008, [0003]; EX1054, 1-2; EX1053, 1, 16.

The first non-exenatide-based, FDA-approved GLP-1 agonist peptide (called liraglutide) more closely adhered to the peptide sequence of human GLP-1 and was administered once daily. EX1050, 1, 11 (Victoza™ approved for diabetes

treatment); EX1013, 1, 14 (Saxenda™ approved for obesity treatment); EX1002, ¶¶79-80; EX1051, Abstract, S59; EX1052, 1435.

The chart below compares prior art amino acid sequences of GIP, GLP-1, liraglutide, and exenatide. Residues colored in green are conserved across all four peptides, and residues appearing differentially in human GIP, human GLP-1, or exenatide are colored in various shades of blue. EX1002, ¶80; EX1053, 1, 16; EX1055, 1-2.

	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		

Subsequent GLP-1 agonists (*e.g.*, dulaglutide, lixisenatide, and semaglutide) were developed with structural modifications to reduce vulnerability to DPP-IV cleavage, reduce immunogenicity, and/or achieve once-weekly dosing. EX1002, ¶¶81-82; EX1056, 1-2, 11; EX1057, 1, 3, 11; EX1058, Abstract, 2.

In the years leading up to 2015, attention had turned to making agonist peptides with dual GIP/GLP-1 activity for treating diabetes and obesity. EX1002, ¶¶83-84; EX1061, 10-11; EX1061, Abstract, 1 (describes dual incretin that acts on the GLP-1 and GIP receptors *in vivo*). The state of the art for GIP and GLP-1 receptor agonisms was well-developed by 2015, permitting the rational design of incretin agonists based on known ligand and receptor structures and structure-activity relationships ("SARs"). EX1002, ¶¶85-90 (discussing EX1062-EX1067, EX1037, EX1030). The literature provided significant predictability about the

amino acid residues that would be employed without unduly sacrificing affinity, activity, or selectivity for the receptors. EX1002, ¶¶87-88, 91; EX1030, 30, 33-34; EX1068, 1021. As Dr. Cornish explains, the prior art described requirements and tolerances for amino acid residues at specific positions. EX1002, ¶91; EX1067, 6276-77 (annotating a SAR of GLP-1 peptide); EX1030, 35; EX1068, 1021. By 2015, artisans were making GIP/GLP-1 receptor dual agonists exhibiting enhanced antihyperglycemic and insulinotropic efficacy as compared to GLP-1 mono-agonists and were turning to the question of improved metabolic stability and duration of action while avoiding unnecessary immunogenicity. EX1002, ¶84; EX1061, Abstract, 1, 10-11.

By 2015, it was routine and well-within the ordinary skill in the art to make new peptides (even by the tens of thousands or more) and evaluate their properties. EX1002, ¶¶66-67; EX1026, Abstract, 824-826 (synthesized 16,200 peptide library for screening); EX1027, 82-83 (enabling rapid evaluation of libraries of millions of peptides for affinity evaluation); EX1028, 541 (techniques to synthesize and screen libraries of more than 1 million members in a matter of weeks improved upon already impressive high-throughput synthesis of >30,000 peptides/year). Moreover, it was common to produce synthetic analogues of naturally occurring peptides to optimize stability against proteolysis, effectiveness, and duration of action (*e.g.*, half-life) of peptide therapeutics. EX1002, ¶¶63-65.

A common approach to extending duration of action of peptides was to conjugate the peptides to a lipophilic moiety. EX1002, ¶65; EX1023, 5 (fatty acid chains to Lys^{20}); EX1024, 475 (site-specific lipidation); EX1025, Abstract; (lipidation improves stability). Although artisans tried PEGylation for increasing peptide half-life, this often created undesirable immune responses. EX1002, ¶65; EX1022, Abstract, 1320 (~25% of healthy blood donors and up to 89% of patients treated with PEGylated drug have anti-PEG antibodies). The first non-exenatide-based, FDA-approved GLP-1 agonist peptide (called liraglutide) thus employed a different approach to improve the half-life of the peptide as compared to native GLP-1. EX1002, ¶79; EX1051, Abstract, S59; EX1052, 1435. Specifically, liraglutide comprises a lipophilic moiety (16-carbon palmitic fatty acid) attached via a $_{\gamma}$glutamic acid ($_{\gamma}$Glu) spacer to the epsilon-amino group of the lysine at position 20 of the peptide. EX1002, ¶79; EX1050, 1, 11-12. Liraglutide was administered as a once-daily injection. EX1052, 1435; EX1050, 1, 11-12.

By December 2014, the prior art disclosed that Novo Nordisk was developing the next-generation GLP-1 receptor agonist semaglutide as a once-weekly injection. EX1002, ¶82; EX1010, 1:21-23. The prior art disclosed that semaglutide employed an albumin-binding moiety ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_{\gamma}$Glu)-CO-$(CH_2)_{16}$-CO_2H) to achieve once-weekly dosing. EX1002, ¶82; EX1009, Example 4; EX1057, 1, 3, 11. Just as with liraglutide, semaglutide was

conjugated at the epsilon-amino group of the lysine at position 20. *Id.* This same moiety was successfully employed to achieve similar or better half-lives in GIP-GLP-1 receptor dual agonists employing the exenatide C-terminal motif. EX1075, Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51 (Table 1), 58 (Table 4); EX1002, ¶98.

Researchers had discovered that appending the exenatide C-terminal motif to GLP-1 receptor agonists or GIP/GLP-1 receptor dual agonists promoted metabolic stability, efficacy, and low immunogenicity. EX1002, ¶¶93-94, 96; EX1072, Abstract, 155-157; EX1069, 8. For example, the literature taught that adding the C-terminal motif to DPP-IV-stabilized GLP-1 maintained potency while increasing half-life, by reducing the rate of peptide clearance through the kidneys and peripheral tissues. EX1002, ¶96; EX1069, 4-6, 8; EX1072, Abstract, 155-57. Researchers applied this same technique to improve proteolytic resistance and insulinotropic activity of GIP while avoiding undesirable lipogenic activity associated with the natural C-terminal sequence of GIP. EX1002, ¶97; EX1074, Abstract, 75-79, 82-84 & Table 1. Researchers then proposed therapeutic treatment of type 2 diabetes through GIP and GLP-1 receptor agonists employing the exendin C-terminal motif. EX1074, Abstract, 84 (glucose-lowering markedly improved when AC163794 administered in combination with AC3174); EX1002, ¶98; EX1075, Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51

(Table 1), 58 (Table 4).

B. WO 2011/119657 A1

The ’657 Publication (EX1007) was published more than one year before the earliest claimed priority date of the challenged patent and is prior art under AIA 35 U.S.C. §102(a)(1). The ’657 Publication was not cited or discussed during prosecution or applied in any rejection.

The ’657 Publication discloses a small collection of GIP analogue peptides that achieve a favorable balance of both GLP-1 and GIP agonisms useful for lowering glucose in type 2 diabetic patients and reducing body weight in obese patients without the nausea that accompanies using GLP-1 agonism alone to full effect. EX1007, Abstract, 1:8-23, 2:5-10; EX1002, ¶¶101-102. Specifically, the ’657 Publication discloses SEQ ID NO:1, which comprises two peptide sequences differentiated from one another by the use of an endogenous Phe (F) amino acid at position 22 or the synthetic amino acid 1-Nal. EX1007, 2:12-25, 5:24-27; EX1002, ¶102.

The present invention provides a peptide comprising the sequence:

Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
5 10
Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-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
Xaa[2]-Xaa[3] (SEQ ID NO:1)

wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated.

The peptides bound and activated both GIPR and GLP-1R with nanomolar or sub-nanomolar strength, even when PEGylated to increase half-life. EX1007, 11:20-19:7 & Tables 1-5; EX1002, ¶¶103-107. Administering the dual agonist peptides to obese mice and rats resulted in dose-dependent weight loss, fat mass loss, reduced food intake, blood glucose reduction, triglyceride reduction, and cholesterol reduction as compared to vehicle. EX1007, 19:8-24:2 & Tables 6-7; EX1002, ¶108. The'657 Publication thus teaches formulating the dual agonist peptides and performing a method of treating diabetes and/or obesity by administering to a patient in need thereof an effective amount of a peptide of the invention. EX1007, 4:26-5:21, 25:4-10 & Claims 13-14; EX1002, ¶109.

C. WO 2013/164483 A1

The ’483 Publication (EX1008) was published more than one year before the earliest claimed priority date of the challenged patent and is prior art under AIA 35 U.S.C. §102(a)(1).

The ’483 Publication teaches that C-terminally-truncated or -substituted GIP/GLP-1 receptor dual agonists are superior to existing and marketed GLP-1 analogues (*e.g.*, liraglutide) for both glycemic control and enhanced weight loss, making them useful for therapy of type 2 diabetes, obesity, and related disorders. EX1002, ¶112; EX1008, [0003]-[0004]. Specifically, the ’483 Publication teaches creating GIP analogues having GIP/GLP-1 dual agonist activity that are truncated after position 28 or substituted with the familiar exenatide C-terminal motif. EX1002, ¶¶115-116, 124; EX1008, [0109]-[0114]. The peptides activated both GIPR and GLP-1R with strengths approaching the endogenous ligands, even when acylated to increase half-life. EX1002, ¶¶113, 115; EX1008, [0109]-[0114]. Administering the peptides to obese animals resulted in identical weight loss to liraglutide at much lower dose and even greater weight reduction with increased dosing. EX1002, ¶114; EX1008, [0117]-[0119] & Figs. 1-7. The ’483 Publication thus teaches formulating C-terminally-truncated or -substituted dual agonists peptides and performing a method of treating diabetes and/or obesity by administering to a patient in need thereof an effective amount of a peptide of the

invention. EX1002, ¶129; EX1008, [0052], [0071], [0077]-[0078], [0085], Claims 28-36, 45-49.

The ’483 Publication’s peptide study further provides SAR data elucidating locations that are amenable to specific substitution. EX1002, ¶¶115-125; EX1008, [0049]-[0050] (table of conservative substitutions). It specifically teaches acylating the peptides through conjugation to the epsilon-amino group of lysine, including at position 20. EX1002, ¶¶126; EX1008, [0054], [0064]-[0066].

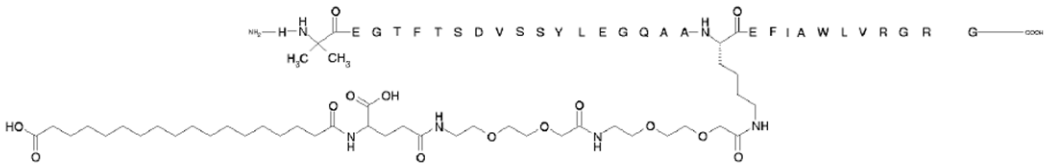
D. WO 2006/097537 A2

The ’537 Publication (EX1009) was published more than one year before the earliest claimed priority date of the challenged patent and is prior art under AIA 35 U.S.C. §102(a)(1). The ’537 Publication was not cited or discussed during prosecution or applied in any rejection.

The ’537 Publication discloses achieving protracted duration of action of GLP-1 receptor peptides by conjugating an albumin binding moiety (([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)-CO-(CH_2)$_{16\text{-}18}$-CO_2H)) to the epsilon-amino group of the lysine amino acid residue at position 20 of the peptide.

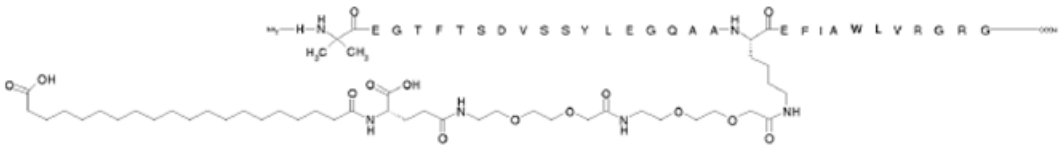
Example 4

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



[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



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

EX1002, ¶¶132-133; EX1009, 47:4-12 (Example 4), 47:12-48:11 (Example 5). Example 4 in the ’537 Publication was identified in the prior art (*e.g.*, EX1010, 1:21-23) in December 2014 as providing the structure for the once-weekly GLP-1-receptor agonist semaglutide in clinical development by Novo Nordisk.

IX. LEGAL STANDARDS

An obviousness analysis involves (1) determining the scope and content of the prior art, (2) ascertaining the differences between the prior art and the claims at issue, (3) resolving the level of ordinary skill in the art, and (4) evaluating any

evidence of secondary considerations. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007).

"[S]tructural similarity between claimed and prior art subject matter, proved by combining references or otherwise, where the prior art gives reason or motivation to make the claimed compositions, creates a *prima facie* case of obviousness, . . . the burden (and opportunity) then falls on an applicant to rebut that *prima facie* case." *In re Dillon*, 919 F.2d 688, 692 (Fed. Cir. 1990) (en banc). "[T]he cases establish that if [a challenger] has found prior art close enough to the claimed invention to give one skilled in the relevant chemical art the motivation to make close relatives (homologs, analogs, isomers, etc.) of the prior art compound(s), then there arises what has been called a presumption of obviousness or a *prima facie* case of obviousness." *Id*. at 696.

"If a person of ordinary skill can implement a predictable variation, §103 likely bars its patentability." *KSR*, 550 U.S. at 417; *Bayer Pharma AG v. Watson Labs., Inc.*, 874 F.3d 1316, 1329 (Fed. Cir. 2017) (obviousness "does not require that the motivation be the best option, only that it be a *suitable* option") (cleaned up); *CRFD Research, Inc. v. Matal*, 876 F.3d 1330 (Fed. Cir. 2017) (design choices are obvious); *Google LLC v. Koninklijke Philips N.V.*, 795 F. App'x. 840, 844-46 (Fed. Cir. 2020) (non-precedential) (affirming obviousness where POSA would have recognized two "evident alternative[s]" even if one alternative was

more efficient than the other).

Moreover, it is well established that a suitable, known alternative need not improve the prior art or even be as good as the prior art to be obvious. *See, e.g.*, *Par Pharm. v. TWI Pharm.*, 773 F.3d 1186, 1197-98 (Fed. Cir. 2014); *In re Fulton*, 391 F.3d 1195, 1200 (Fed. Cir. 2004); *Merck & Co. v. Biocraft Labs.*, 874 F.2d 804, 807 (Fed. Cir. 1989); *In re Mouttet*, 686 F.3d 1322, 1334 (Fed. Cir. 2012). Indeed, providing a predictable variation of a known solution is obvious. *See, e.g.*, *Tyco Healthcare Group v. Ethicon Endo-Surgery*, 774 F.3d 968, 977 (Fed. Cir. 2014); *Spectrum Pharm. v. Sandoz Inc.*, 802 F.3d 1326, 1335 (Fed. Cir. 2015); *In re Fout*, 675 F.2d 297, 301 (Fed. Cir. 1982). Here, the suggestion in the art to make and use the claimed compounds is not undermined in any way by the possibility that a POSA could also make other GIP/GLP-1 receptor dual agonist compounds due to the ease with which peptides were synthesized and tested for activity.

Unexpected results must be based on comparison with the closest prior art and must represent a difference in kind rather than a difference of degree. *In re Harris*, 409 F.3d 1339, 1344 (Fed. Cir. 2005) ("The 32-43% increase in stress-rupture life, however, does not represent a 'difference in kind' that is required to show unexpected results.").

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

As explained in detail further below, the prior art teaches or suggests every

element of each challenged claim in the claimed configuration, and provides good reason to make the claimed compounds and use the claimed methods with a reasonable expectation of success. The prior art thus renders obvious each claim as a whole.

The ’657 and ’483 Publications both teach successfully making GIP analogues useful for GIP/GLP-1 receptor dual agonism, including for the treatment of diabetes and obesity. *See, e.g.*, EX1007, Abstract; EX1008, Abstract; EX1002, ¶¶101, 109; 111-114, 129. The ’483 Publication teaches a genus of GIP/GLP-1 receptor dual agonists that essentially encompasses the N-terminal peptide sequence of the ’657 Publication, but succeeds in creating dual receptor agonism by truncating the peptide after position 28 or by substituting the C-terminal residues with the familiar exenatide C-terminal motif. EX1008, [0007], [0017]; EX1002, ¶128; *see also* EX1002, ¶147 & n.280. The structure-activity relationship in the ’483 Publication suggests applying the familiar exenatide C-terminal motif to the ’657 Publication’s sequence will make a useful GIP/GLP-1 receptor dual agonist. EX1002, ¶¶124, 139-140.

The ’483 Publication further teaches acylating the peptide through conjugation to the epsilon-amino group of a lysine (including at position 20) to prolong duration of action. EX1008, [0006], [0027], [0056]-[0058], [0063]-[0066]; EX1002, ¶¶120, 126. The ’537 Publication teaches conjugation of the known

albumin-binding moiety (([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)-CO-$(CH_2)_{16\text{-}18}$-CO_2H)) to the epsilon-amino group of the lysine amino acid residue at position 20 prolongs the duration of action of the GLP-1 agonist semaglutide, thereby achieving once-weekly dosing. EX1009, Examples 4-5; EX1002, ¶¶130-133; EX1010, 1:21-23. Based on the known structure-activity-relationships for GIP/GLP-1 receptor dual agonism and the known and successful use of the claimed albumin-binding moiety to impart protracted duration of action, a skilled artisan had good reason with a reasonable expectation of success to conjugate the albumin-binding moiety to Lys^{20} of the peptide. EX1002, ¶¶135-136. In view of the combined teachings of the prior art, each challenged claim was thus obvious by January 2015.

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 X_1 is Aib

X_2 is Aib…

X_3 is Phe or 1-Nal;

Claimed peptide sequences are obvious over the combined teachings of the ’657, ’483, and ’537 Publications.

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

The ’657 Publication discloses a most promising GIP/GLP-1 dual agonist peptide sequence useful for treating diabetes and/or reducing body weight. EX1007, Abstract, 2:12-25, 5:24-27, Claims 1-12.

> The present invention provides a peptide comprising the sequence:
>
> Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu-
> 5 10
> Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-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
> Xaa[2]-Xaa[3] (SEQ ID NO:1)
>
> wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated.

The ’657 Publication teaches dual agonist peptides effectively reduced body weight and glucose sensitivity and were desirable for their ability to do so potently without as much nausea as GLP-1 mono-agonists. EX1007, 2:5-10, 11:20-27, 1:8-23. The ’657 Publication relies on *in vitro* and *in vivo* data to demonstrate SEQ ID NO:1 has utility as a GIP/GLP-1 dual agonist, including for glycemic control and weight loss. EX1007, 13:7-8, 15:1-3, 17:1-19:7, 22:15-30 & Tables 1-7. As Dr.

Cornish explains, the disclosures of the ’657 Publication provided a POSA with good reason to make and evaluate structurally similar peptide sequences likely to share GIP/GLP-1 receptor dual agonism utility with the disclosed SEQ ID NO:1. EX1002, ¶¶144, 137-138. 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, including use of the exenatide C-terminal motif and Lys^{20}-conjugation to a promising albumin-binding moiety. EX1002, ¶¶139, 144, 114, 135.

b. Exenatide C-Terminal Motif Useful For GIP/GLP-1 Agonists

As Dr. Cornish explains, a POSA had very good reason to look to prior art GIP/GLP-1 dual agonism structure-activity-relationship information for structurally-similar GIP analogues to build upon and even improve SEQ ID NO:1. EX1002, ¶¶145; *see* also Section VIII.A *supra* (discussing ease of synthesizing new peptides and extensive knowledge about SAR for GIP/GLP-1 agonism). The ’483 Publication teaches GIP/GLP-1 dual agonism SAR information for GIP analogues similar to and overlapping with those disclosed in the ’657 Publication, except that it teaches deleting the amino acid residues at positions 30-42 or substituting with the familiar exenatide C-terminal motif. 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 VIII.A & B, EX1069, Abstract, 7-8 (exenatide C-terminal motif); EX1002, ¶¶146-49 (truncation and C-terminal replacement works *in vitro* and *in vivo*). The prior art thus suggests modifying 42-amino-acid-residue dual agonists to be approximately the same length as endogenous GLP-1 (i.e., truncating to 28-31 residues) or to substitute with the exenatide C-terminal sequence. EX1002, ¶¶150.

A POSA further would have recognized additional benefits of substituting exenatide's C-terminal motif in place of the foreign C-terminal motif employed in SEQ ID NO:1. EX1002, ¶¶151-152. For example, exenatide's C-terminal motif was associated with reduced clearance mechanisms and increased metabolic stability without unduly sacrificing activity. EX1002, ¶¶77, 96; EX1048, 3587, Figure 1; EX1072, Abstract, 155-157. As discussed above (Section VIII.A), this same motif was successfully appended to DPP-IV-resistant GLP-1 and to GIP to improve metabolic stability while retaining favorable potency. EX1002, ¶¶96-98. EX1073, Abstract, 17-21 & Table 2; EX1074, Abstract, 75-79, 82-84 & Table 1.

As Dr. Cornish explains, a POSA would have had a reasonable expectation that the resulting peptide would function well as a GIP/GLP-1 receptor dual agonist based on the *in vitro* and *in vivo* data used to construct the SAR from the ’657 and ’483 Publications. EX1002, ¶¶137. As shown in Tables A-B below, which sort the top dual agonist peptides tested in the ’483 Publication respectively by GIP or GLP-1 potency and presents them together with the sequences of endogenous and FDA-approved agonists, employing the exenatide C-terminal motif was very compatible with effective dual agonism. EX1002, ¶¶146-148, & Tables A-B (*see* next page).

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	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					
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				0.0068	0.015
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				0.0071	0.0087
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															0.0083	0.011
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															0.0091	0.017
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															0.0097	0.018
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				0.0099	0.015
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															0.011	0.022
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				0.012	0.018
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															0.013	0.011
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															0.015	0.022
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															0.015	0.0073
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															0.016	0.013
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															0.021	0.0074
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															0.022	0.020
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	S	NH2					0.024	0.0088
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				0.028	0.022
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															0.031	0.023
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				0.035	0.031
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															0.036	0.0087
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				0.037	0.033
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															0.045	0.031
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															0.049	0.0090

Green = conserved across peptides

Light Blue = GIP

Dark Blue = GLP-1

Light Purple = Exenatide

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	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	R	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	S	NH2				
Compound 28	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	S	NH2		0.020	0.0051
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										0.015	0.0073
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										0.021	0.0074
Compound 24	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	Aib	K	NH2											0.096	0.0085
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	S	NH2		0.0071	0.0087
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										0.036	0.0087
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	S	NH2			0.024	0.0088
Compound 30	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	K	K	A	Q	K	E	F	V	N	W	L	L	A	Q	K	NH2										0.054	0.0093
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											0.0083	0.011
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	A	Aib	K	NH2										0.013	0.011
Compound 16	Y	Aib	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	Aib	K	NH2										0.053	0.012
Compound 23	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	K	A	Aib	K	NH2										0.42	0.012
Compound 42	Y	Aib	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	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	NH2											0.016	0.013
Compound 9	Y	Aib	E	G	T	F	T	S	D	L	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2										0.091	0.014
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		0.0068	0.015
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	S	NH2		0.0099	0.015
Compound 18	Y	Aib	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	Aib	K	NH2										0.36	0.015
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											0.0091	0.017
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											0.0097	0.018
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		0.012	0.018
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											0.0070	0.018
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											0.011	0.022
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										0.015	0.022
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		0.028	0.022
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										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	Aib	K	NH2										0.21	0.024
Compound 8	Y	Aib	E	G	T	F	S	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2										0.10	0.029
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	S	NH2		0.035	0.031
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											0.045	0.031
Compound 13	Y	Aib	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	Aib	K											0.14	0.032
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	S	NH2		0.037	0.033
Compound 48	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											0.061	0.041
Compound 25	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	Y	G	Nal	L	D	F	NH2				0.12	0.041
Compound 46	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											0.088	0.048
Compound 49	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	D	F	I	E	W	L	E	S	A	NH2											0.092	0.049

The *in vivo* data in the ’483 Publication likewise indicated the exenatide C-terminal motif resulted in favorable efficacy. EX1002, ¶¶149-150, 153. Indeed, compounds achieved superior results in lowering glucose and body weight compared to liraglutide, even using much lower doses, even without having the lowest (most potent) EC_{50} results in the tables. EX1008, [0117]-[0119] & Figs. 1-7

EX1002, ¶149 (annotated Figs. 1-2. reproduced right). As one example, Compound 33 achieved comparable body weight reductions to liraglutide using one-fifth of the dose (red & green annotations), and achieved greater weight reduction with additional dosing (magenta and blue annotations). *See, e.g.*, EX1008, Fig. 2 (right). Accordingly, there was a reasonable expectation that modifying the SEQ ID NO:1

Figure 1

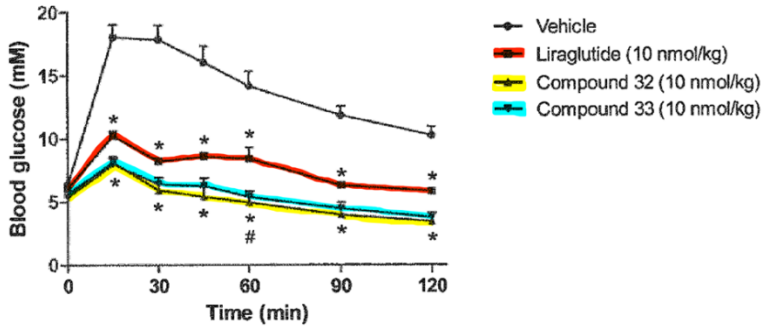
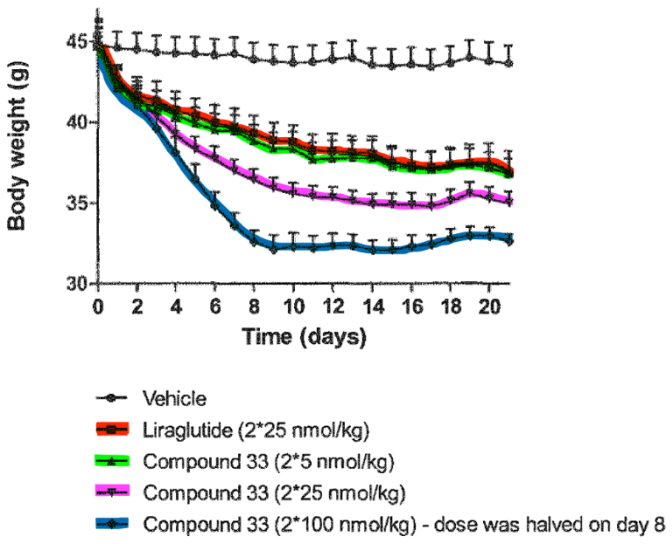


Figure 2:

A



peptide sequence with the familiar exenatide C-terminal motif would result in a useful and effective GIP/GLP-1 receptor dual agonist.

The reasonable expectation of effective GIP/GLP-1 receptor dual agonism in the resulting peptide is further confirmed by the ’483 Publication’s SAR. As Dr. Cornish explains, Table C (next page) 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 of SEQ ID NO:1 for GIP/GLP-1 receptor dual agonism in connection with the exenatide C-terminal motif. EX1002, ¶154.

	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	F or NaL	V	Q	W	L	I	A	Aib	K	K	Q	Q	K	H	Q	I	T	Q	C or N/A	C or N/A	
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		
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	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											

Table C

Green = conserved across peptides

Light Blue = GIP

Dark Blue = GLP-1

Light Purple = Exenatide

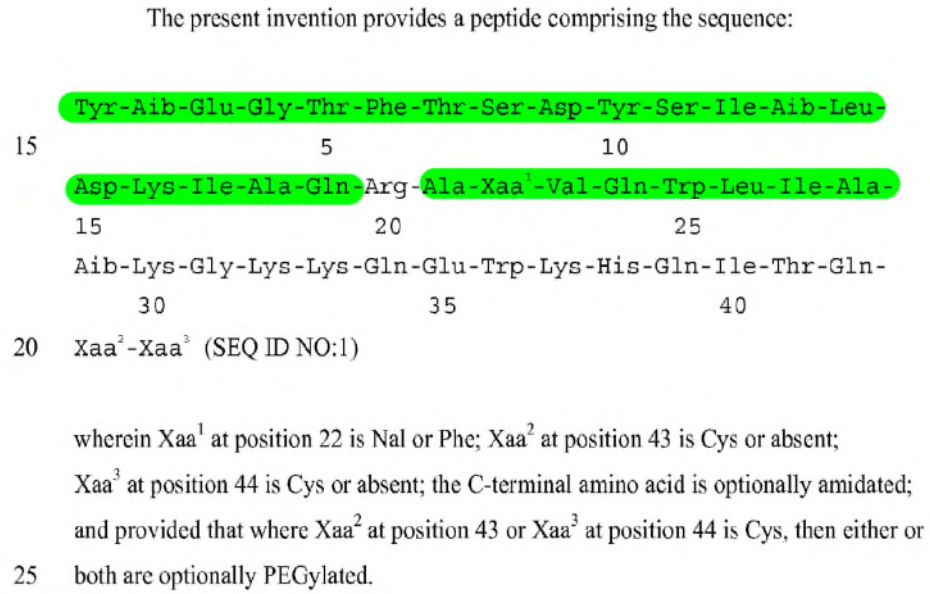
As Dr. Cornish explains, SEQ ID NO:1's first 28 amino acid residues fit well within the GIP/GLP-1 receptor dual agonism SAR in the '483 Publication. EX1002, ¶¶147 n.280, 154-158; *see also* EX1002, ¶¶115-124 (SAR discussion. This remains true for residues like Ala^{21} (which appear repeatedly in Table C), as well as for residues like Gln^{24} and Ile^{27} (which do not appear in Table C but are consistent with the SAR of the '483 Publication as evidenced by its express teachings). EX1002, ¶¶155-157. For example, the '483 Publication specifically identifies Gln as an appropriate substitution for each of E (Glu) and N (Asn) (EX1008, [0049]-[0050]), both of which are shown to work quite well at position 24, and are consistent with the known ligand-receptor interactions. EX1002, ¶¶155-156, 120; *see* Section VIII.A above. The '483 Publication thus corroborates the '657 Publication's use of Q at position 24.

As another example, the '483 Publication likewise corroborates the disclosure of the '657 Publication of successfully employing isoleucine (Ile, I) at position 27. EX1002, ¶¶157. Indeed, the '483 Publication expressly discloses the use of I at position 27. *See, e.g.*, EX1008, [0007]. As Dr. Cornish explains, successful use of Ile^{27} is fully consistent with the working examples in the '483 Patent, which successfully employed the Leu and Val amino acid residues at that location (demonstrating functional homology compatible with Ile^{27}). EX1002, ¶¶157, 119. Further, the '483 Publication expressly discloses (EX1008, [0049]-

[0050]) that Ile is a conservative substitution within its SAR for both L and V. EX1002, ¶157 n.301. Accordingly, the '483 Publication further supports the reasonable expectation for efficacious GIP/GLP-1 receptor dual agonism when employing residues 1-28 of SEQ ID NO:1 together with the exenatide C-terminal GGPSSGAPPPS motif. EX1002, ¶158.

Beyond the foregoing, a POSA had additional good reasons to use the exenatide C-terminal motif as a whole beginning at position 29. For example, Dr. Cornish explains that 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. EX1002, ¶¶150-151. This unnatural sequence was potentially undesirable as it raised the risk of high immunogenicity and the elicitation of anti-drug antibodies. *Id.* Substituting in the full exenatide C-terminal motif beginning at position 29 would avoid unnecessary use of the non-natural (and potentially immunogenicity-inducing) Aib at position 29 by employing the Gly found naturally in endogenous GLP-1 and in FDA-approved GLP-1 receptor agonists exenatide and liraglutide, which are known to elicit low-titer anti-drug antibodies consistent with therapeutic efficacy. EX1002, ¶¶80, 94, 151; EX1070, Abstract (exenatide safety); EX1071, Abstract, 1700-1701 (low frequency and magnitude liraglutide antibody formation); EX1009, 47:4-28, (endogenous GLP-1

with G at position 29), 4:32-5:3 (invoking Exendin-4 sequence); EX1069, 8 (exendin sequence); EX1053, 16 (low immunogenicity); EX1054, 1-2, 9 (exenatide sequence; low immunogenicity). This was fully consistent with the SAR provided by the'483 Publication for dual receptor agonism. EX1002, ¶¶115-125; EX1008, [0007]. Accordingly, a POSA had good reason and reasonable expectation of success to replace the foreign C-terminal amino acid residues of SEQ ID NO:1 beginning at position 29 with the natural and FDA-approved exenatide C-terminal motif to make a GIP/GLP-1 receptor dual agonist having metabolic stability and favorable potency without undue immunogenicity. EX1002, ¶¶150-152, 158.

Claim 1[a]	Prior Art
A compound of Formula: 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 X_1 is Aib X_2 is Aib… X_3 is Phe or 1-Nal;	**The '657 Publication teaches:** Efficacious GIP/GLP-1 receptor dual agonist sequence for treatment of diabetes and obesity:  The present invention provides a peptide comprising the sequence: Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-Val-Gln-Trp-Leu-Ile-Ala- Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln- Xaa[2]-Xaa[3] (SEQ ID NO:1) wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated. EX1007, 2:12-25 (claimed sequence residues highlighted in green). **The '483 Publication teaches:** 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. "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." EX1008, [0006]. "[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." EX1008, [0024]

"[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."). EX1008, [0025].

Table A
Data From EX1008, [0109], [0115], Tables 1, 3 (GIP Sort)

	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	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	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	S	G	A	P	P	P	S	NH2		0.0068	0.015
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	S	G	A	P	P	P	S	NH2		0.0071	0.0087
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													0.0083	0.011
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													0.0091	0.017
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													0.0097	0.018
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		0.0099	0.015
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													0.011	0.022
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	A	G	P	S	S	G	A	P	P	P	S	NH2		0.012	0.018
Compound 41	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	R	F	V	E	W	L	L	S	A	NH2													0.013	0.011
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													0.015	0.022
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													0.015	0.0073
Compound 44	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	S	K	A	A	H	R	F	V	E	W	L	L	R	A	NH2													0.016	0.013
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													0.021	0.0074
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													0.022	0.020
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	S	NH2			0.024	0.0088
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		0.028	0.022
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													0.031	0.023
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		0.035	0.031
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													0.036	0.0087
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		0.037	0.033
Compound 34	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	E	K**	A	A	K	E	F	V	E	W	L	E	S	A	NH2													0.045	0.031
Compound 20	Y	Aib	E	G	T	F	T	S	D	Y	S	I	F	L	D	K	K	A	Q	R	A	F	V	K	W	L	L	A	Aib	K	NH2													0.049	0.0090

Table B
Data From EX1008, [0109], [0115], Tables 1, 3 (GLP-1 Sort)

	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	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	S	G	A	P	P	P	S	NH2			
Compound 28	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	S	G	A	P	P	P	S	NH2		0.020	0.0051
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													0.015	0.0073
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													0.021	0.0074
Compound 24	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	Aib	K	NH2													0.096	0.0085
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	S	G	A	P	P	P	S	NH2		0.0071	0.0087
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													0.036	0.0087
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	S	NH2			0.024	0.0088
Compound 30	Y	Aib	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	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													0.0083	0.011
Compound 41	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	E	S	K	A	A	H	R	F	V	E	W	L	L	S	A	NH2													0.013	0.011
Compound 16	Y	Aib	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	Aib	K	NH2													0.053	0.012
Compound 23	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	K	A	Aib	K	NH2													0.42	0.012
Compound 42	Y	Aib	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	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													0.016	0.013
Compound 9	Y	Aib	E	G	T	F	T	S	D	L	S	I	Y	L	D	K	K	A	Q	R	A	F	V	N	W	L	L	A	Aib	K	NH2													0.091	0.014
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		0.0068	0.015
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		0.0099	0.015
Compound 18	Y	Aib	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	Aib	K	NH2													0.36	0.015
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													0.0091	0.017
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													0.0097	0.018
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		0.012	0.018
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													0.0070	0.018
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													0.011	0.022
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													0.015	0.022
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		0.028	0.022
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													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	Aib	K	NH2													0.21	0.024
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													0.10	0.029
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		0.035	0.031
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													0.045	0.031
Compound 13	Y	Aib	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	Aib	K														0.14	0.032
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		0.037	0.033
Compound 48	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	E	S	A	NH2													0.061	0.041
Compound 25	Y	Aib	E	G	T	F	T	S	D	Y	S	I	Y	L	D	K	K	A	Q	R	A		V	N	W	L	L	A	Aib	K	Y	G	Nal	L	D	F	NH2					0.12	0.041
Compound 46	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													0.088	0.048
Compound 49	Y	Aib	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

Figure 1

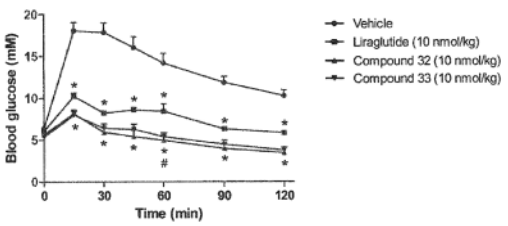
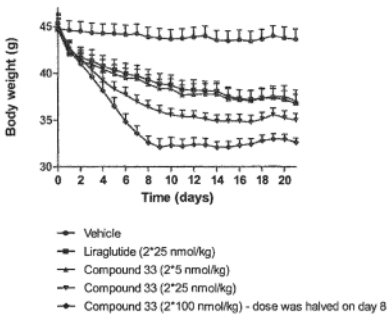


Figure 2:

A



GIP, GLP-1, and GLP-1 receptor agonists liraglutide (Victoza™) and exenatide (Byetta™, Bydureon™) all were known, and dual

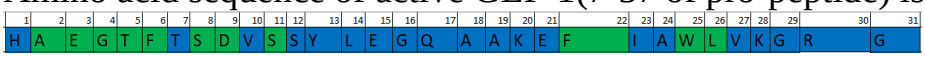
agonism was desirable.

"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-lowing and insulinotropic effects compared to treatment with Liraglutide and GIP alone[.]" EX1008, [0002]-[0003].

"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**." EX1008, [0004].

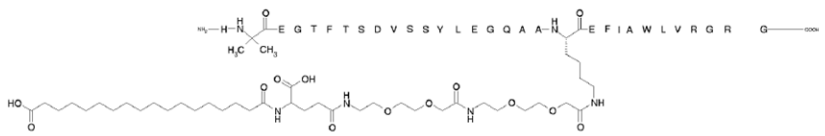
The '537 Publication teaches:

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



Example 4

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



[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

EX1009, 47:4-28; *see also* EX1009, 3:8-17 (Lys28 in

	endogenous GLP-1), 4:1-2 (SEQ ID NO:1 provides GLP-1(7-37). Amino acid sequence of Exendin-4 (exenatide) was known. "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." EX1009, 4:32-5:3; *see also* Section VIII.A above.

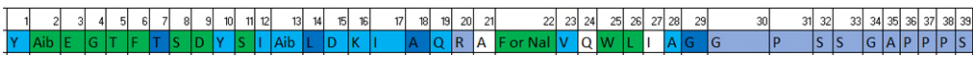
c. Lys^{20}

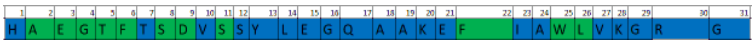
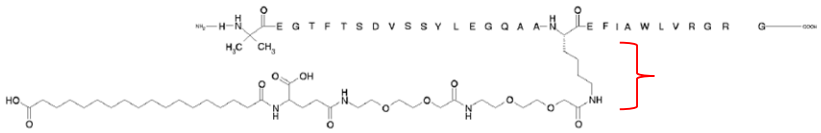
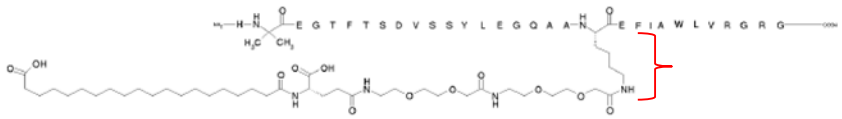
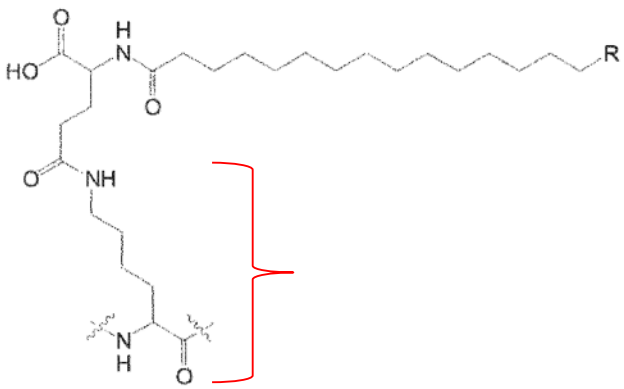
Both the '483 and '537 Publications teach use of Lys^{20} in the agonist peptides for conjugation to an albumin-binding moiety to provide a longer *in vivo* duration of action. EX1002, ¶¶159-162. The '537 Publication teaches Lys^{20}-conjugation is desirable for insulinotropic agents generally and GLP-1 agonists in particular. EX1009, 1:5-24, 2:10-13, 3:8-4:8, 6:6-21; EX1002, ¶159.

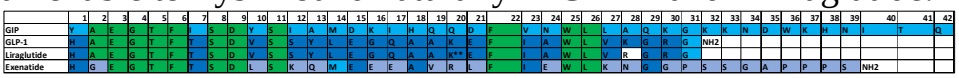
The '483 Publication also specifically teaches employing Lys^{20} as a location for conjugation, but for GIP/GLP-1 receptor dual agonist peptides. EX1008, [0064]-[0067]; EX1002, ¶161. The '483 Publication discloses that conjugation of dual agonist peptides at the epsilon amino of lysine improves the half-life of the peptide. EX1008, [0006]. It also 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." EX1008, [0056]. Moreover, employing Lys^{20} in the peptide is consistent both with the SAR of the '483 Publication (i.e., many effective dual agonists in Tables A and B employ Lys^{20}) and with its express suggestion to acylate GIP/GLP-1 receptor dual agonists at Lys^{20}. EX1002, ¶161.

In view of common prior art usage of Lys^{20} for conjugation, including the disclosures of the '537 Publication and the '483 Publication, a POSA had good reason with reasonable expectation of success to employ Lys^{20} in the peptide appending the familiar exenatide C-terminal motif to the first 28 amino acid residues of SEQ ID NO:1 of the'657 Publication. EX1002, ¶162. Accordingly, a POSA had good reason to make and use an amino acid sequence (shown below) falling within the scope of claim 1. *Id.*



Claim 1[a]	Prior Art
A compound of Formula: 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 X_1 is Aib X_2 is Aib… X_3 is Phe or 1-Nal;	**The '537 Publication teaches:** Use of Lys^{20} to facilitate conjugation to albumin-binding moiety.  **Example 4** N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.  [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**  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:4-28. **The '483 Publication teaches:** Use of Lys^{20} to facilitate conjugation to albumin-binding moiety. "The amino acid side chain to which the lipophilic substituent is conjugated…may be a **side chain of a Lys**, Glu or Cys residue." EX1008, [0064]. "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 $_{\gamma}$Glu spacer (Z^2) via an amide linkage." EX1008, [0065]-[0066]. "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." EX1008, [0067]. "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…." EX1008, [0006]. *See also* SAR Tables above showing dual agonism SAR was very amenable to Lys^{20} 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
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		

2. Albumin-Binding Moiety

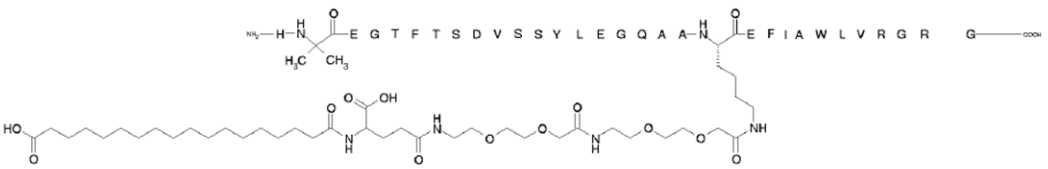
…K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)2-($_{\gamma}$Glu)a-CO-(CH2)b-CO2H wherein a is 1 to 2 and b is 10 to 20…

The '537 Publication discloses the claimed albumin-binding moiety. EX1002, ¶¶163-165. In particular, it discloses chemically modifying Lys^{20} through conjugation of the albumin-binding moiety ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_{\gamma}$Glu)$_1$-CO-$(CH_2)_{16\text{-}18}$-CO_2H to the epsilon-amino group of the Lys^{20} sidechain. For

illustrative purposes, Examples 4 and 5 disclose chemically modifying Lys^{20} of the GLP-1 receptor agonist semaglutide through conjugation of the albumin-binding moiety ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)$_1$-CO-$(CH_2)_{16\text{-}18}$-CO_2H to the epsilon-amino group of the Lys^{20} sidechain. EX1009, 47:4-12 (Example 4), 47:12-48:11 (Example 5); *see also* EX1009, 17:1-10, 20:6-9. 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 moieties satisfy the albumin-binding moiety limitation of claim 1, including with respect to the location and manner of attachment to the peptide. EX1002, ¶163.

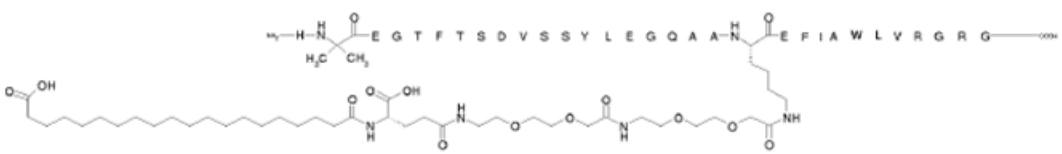
Example 4

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



[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

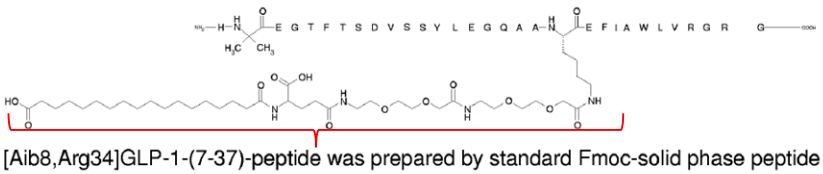
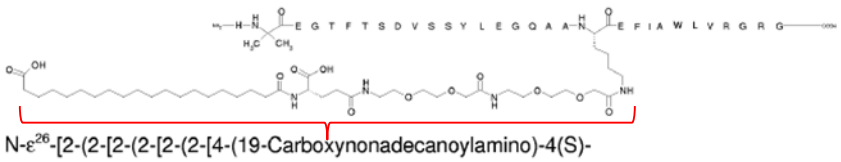
Example 5

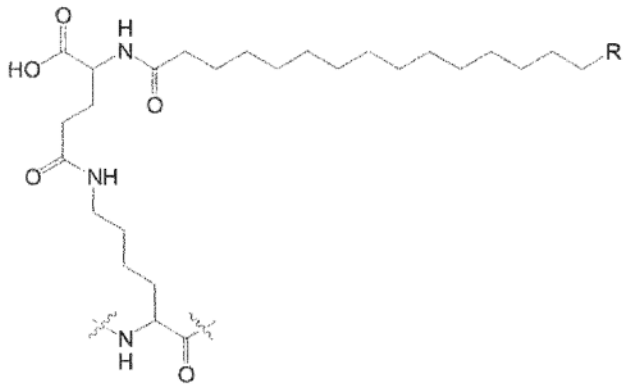


N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

As Dr. Cornish confirms, a POSA had good reason to employ the prior art albumin-binding moiety 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. EX1002, ¶¶164-165. As just discussed, both the ’537 and ’483 Publications teach conjugating the albumin-binding moiety to the epsilon amino group of Lys^{20}. EX1009, 2:1-4; EX1008, [0006], [0056]-[0058], [0061]-[0061], [0063]-[0067]. The ’537 Publication teaches reducing peptide dosing frequency for the treatment of diabetes and obesity because patients find injections unpleasant. EX1009, 1:25-34. It presents Lys^{20}-conjugation of the albumin-binding moiety to provide longer *in vivo* duration of action to insulinotropic 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. EX1009, 1:5-24, 2:10-13, 3:8-4:8, 6:6-21. These teachings are consistent with those of the ’483 Publication. EX1002, ¶¶161, 165. But, the albumin-binding-moiety used in the ’537 Publication achieved once-weekly dosing. *See, e.g.*, EX1010, 1:21-23; EX1009, Example 4. In contrast, Lys^{17}-conjugation of compounds 32 and 33 of the ’483 Publication using fatty acids and the $_{\gamma}$Glu linker but without using the linker of the ’537 Publication achieved a half-life of 3.4-3.7 hours in mice. EX1008, [0116] (Table 4). A POSA thus had good reason with a reasonable expectation of success to use the albumin-

binding moiety that achieved protracted duration of action for semaglutide to achieve once-weekly dosing of the GIP/GLP-1 receptor dual agonist, or at least improve its protracted duration of action to be comparable to liraglutide, exenatide, or other prior art GIP/GLP-1 receptor agonists. EX1002, ¶¶114, 165; *see also* Section VIII.A above.

Claim 1[b]	**Prior Art**
…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)$_2$-($_\gamma$Glu)α-CO-(CH$_2$)$_b$-CO$_2$H wherein α is 1 to 2 and b is 10 to 20…	**The '537 Publication teaches:** 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)$_2$-($_\gamma$Glu)$_1$-CO-(CH$_2$)$_{16-18}$-CO$_2$H. **Example 4** N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.  [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**  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:4-26. **The '483 Publication teaches:** Conjugation to albumin-binding moiety protracts duration of action. "[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." EX1008, [0056]. b is 10 to 24 and a is 1 "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." EX1008, [0061] "The **spacer** may be, for example, **…$_{\gamma}$Glu**…." EX1008, [0064]. "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 $_{\gamma}$**Glu spacer** (Z^2) via an amide linkage." 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.

Both the '657 and '483 Publications disclose the C-terminal amino acid is amidated as a C-terminal primary amide. EX1007, 2:23-31 ("the C-terminal amino acid is optionally amidated"); EX1008, 65-67 (Table 1 showing compounds with

C-terminal primary amide). The ’483 Publication also disclose the use of pharmaceutically acceptable salts of the peptides. EX1008, [0081] (“salts or solvates thereof, in a pharmaceutically acceptable carrier”), [0084] (“pharmaceutically acceptable salt”). Accordingly, this element is satisfied by the prior art. EX1002, ¶166.

Claim 1[c]	Prior Art
…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.	**The ’657 Publication teaches:** The C-terminal amino acid is optionally amidated. “[T]he C-terminal amino acid is optionally amidated[.]” EX1007, 2:23. **The ’483 Publication teaches:** GIP/GLP-1 receptor dual agonist compounds having C-terminal primary amide. **Table 1.** **Compound No.** — **Sequence** 1 — Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2 2 — Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2 3 — Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2 4 — Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2 5 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 **Table 2.** **Compound No.** — **Sequence** 6 — pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 7 — Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 8 — Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 9 — Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 10 — Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 11 — Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2 12 — Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2 13 — Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2 14 — Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2 15 — Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2 16 — Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2 17 — Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2 18 — Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2 19 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2 20 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2 21 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2 22 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLSA-Aib-K-NH_2 65 EX1008, 65-67 (Tables 1-2). Use of pharmaceutically acceptable salts of peptides. “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**.” EX1008, [0081]. “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." EX1008, [0084].

The combined teachings of the asserted references thus teach, suggest, or render obvious each element of claim 1 and the compound of claim 1 as a whole. EX1002, ¶167.

B. Claim 2

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

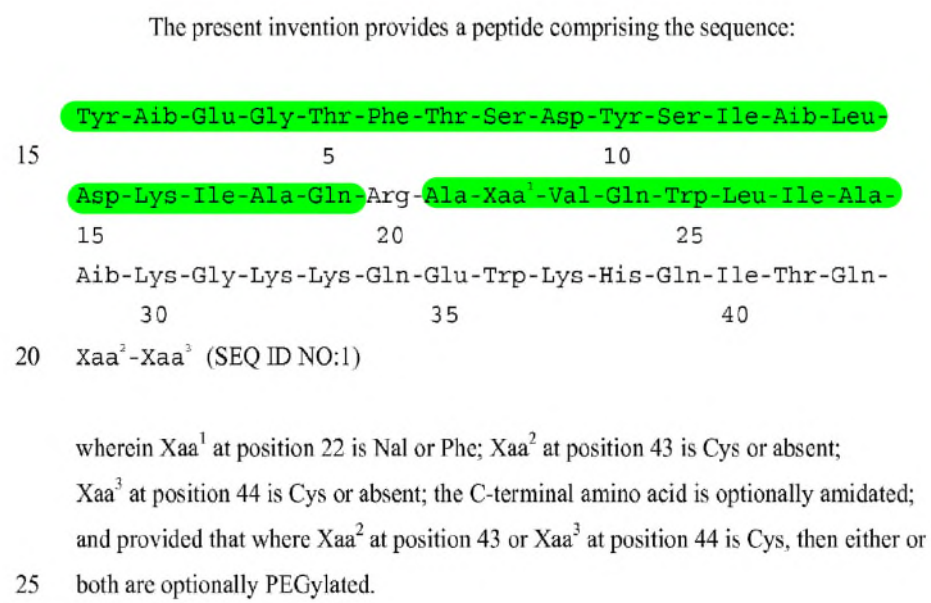
Section X.A above establishes the subject matter of claim 1 was obvious. Claim 2 was obvious for the same reasons. While claim 2 is limited to Phe^{22}, rather than $1\text{-}Nal^{22}$, this is expressly disclosed for GIP/GLP-1 receptor dual agonism in both the '657 and '483 Publications, as discussed above. Claim 2 as a whole was thus obvious. EX1002, ¶168.

Claim 2	Prior Art
X_3 is Phe	**The '657 Publication teaches:** Phe[22]: The present invention provides a peptide comprising the sequence: Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-Val-Gln-Trp-Leu-Ile-Ala- Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln- Xaa[2]-Xaa[3] (SEQ ID NO:1) wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated. EX1007, 2:12-25 (claimed sequence residues highlighted in green).

C. Claim 3

3. The compound of claim 1, wherein X_3 is 1-Nal.

Section X.A above establishes the subject matter of claim 1 was obvious. Claim 3 was obvious for the same reasons. While claim 2 is limited to 1-Nal[22] rather than Phe[22], this is expressly disclosed for GIP/GLP-1 receptor dual agonism in both the '657 and '483 Publications, as discussed above. Claim 3 as a whole was thus obvious. EX1002, ¶169.

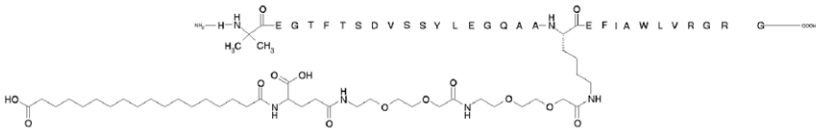
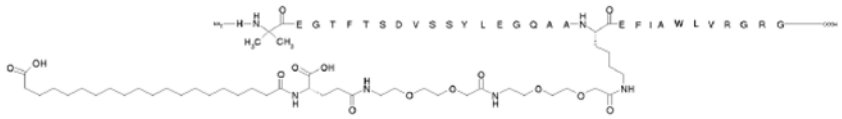
Claim 3	Prior Art
X_3 is 1-Nal	**The '657 Publication teaches:** 1-Nal[22]:  The present invention provides a peptide comprising the sequence: Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-Val-Gln-Trp-Leu-Ile-Ala- Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln- Xaa[2]-Xaa[3] (SEQ ID NO:1) wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated. EX1007, 2:12-25 (claimed sequence residues highlighted in green).

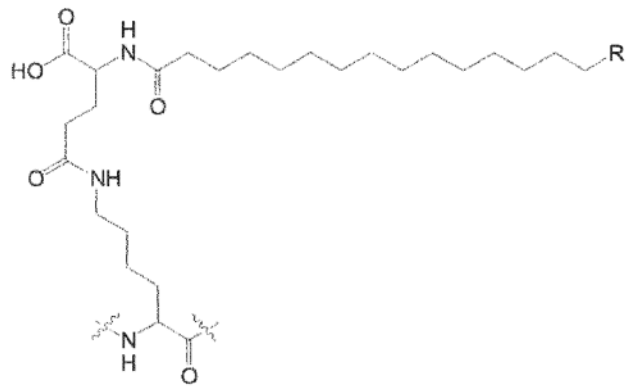
D. Claim 4

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

Section X.A above establishes the subject matter of claim 1 was obvious. Section X.B establishes the subject matter of claim 2 was obvious. Claim 4 was obvious for the same reasons. While claim 4 is limited to b is 14 to 18, rather than 10 to 20, this is expressly disclosed in the '537 Publication, as discussed above. For example, the '537 Publication Examples 4-5 disclose b is 16 and 18 respectively, satisfying the limitation "wherein b is 14 to 18." EX1009, 47:4-26.

This is consistent with the disclosures of the'483 Publication as well. Claim 4 as a whole was thus obvious. EX1002, ¶170.

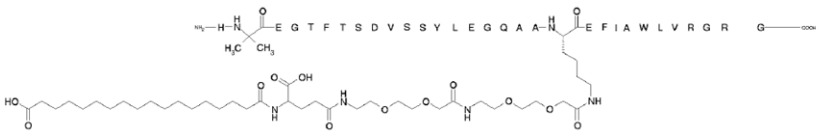
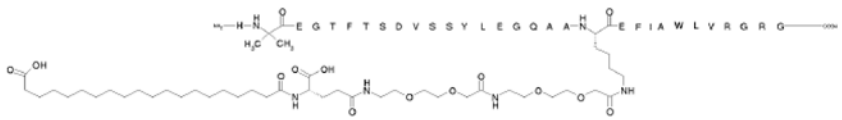
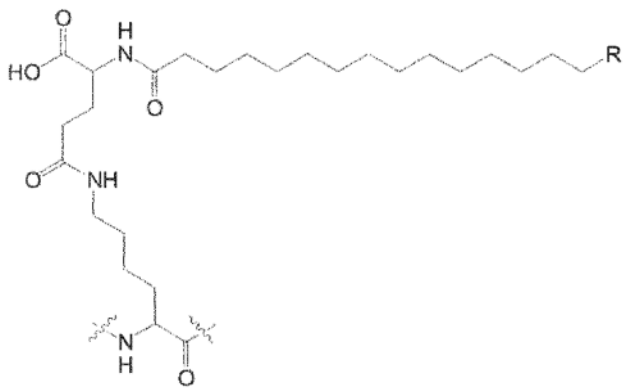
Claim 4	Prior Art
b is 14 to 18	**The '537 Publication teaches:** b is 16 or 18 **Example 4** N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.  [Aib8,Arg34]GLP-1-(7-37)-peptide was prepared by standard Fmoc-solid phase peptide synthesis and purified by preparative HPLC. [Aib8,Arg34]GLP-1-(7-37)-peptide was **Example 5**  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:4-26. **The '483 Publication teaches:** b is 14 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." EX1008, [0061]. "An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:

	 EX1008, [0065].

E. Claim 5

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

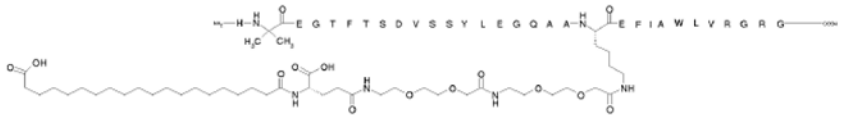
Section X.A above establishes the subject matter of claim 1 was obvious. Section X.D establishes the subject matter of claim 4 was obvious. Claim 5 was obvious for the same reasons. While claim 5 is limited to b is 16 to 18, rather than 14 to 18, this is expressly disclosed in the ’537 Publication, as discussed above. For example, the ’537 Publication Examples 4-5 disclose b is 16 and 18 respectively, satisfying the limitation “wherein b is 14 to 18.” EX1009, 47:4-26. This is consistent with the disclosures of the’483 Publication as well. EX1008, [0061], [0065]. Claim 5 as a whole was thus obvious. EX1002, ¶171.

Claim 5	Prior Art
b is 16 to 18	**The ’537 Publication teaches:** b is 16 or 18 **Example 4** N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.  [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**  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:4-26. **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.” EX1008, [0061] “An example of a lipophilic substituent comprising a lipophilic moiety Z^1 and spacer Z^2 is shown in the formula below:  EX1008, [0065].

F. Claim 6

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

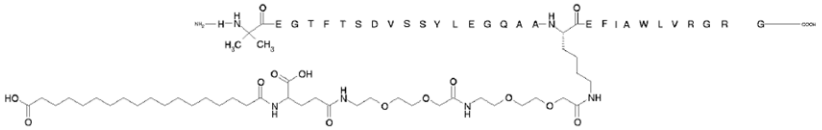
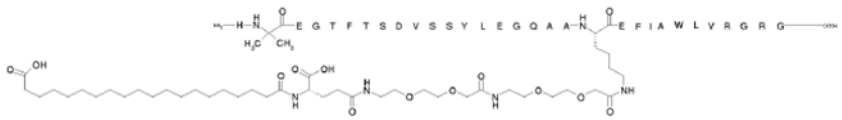
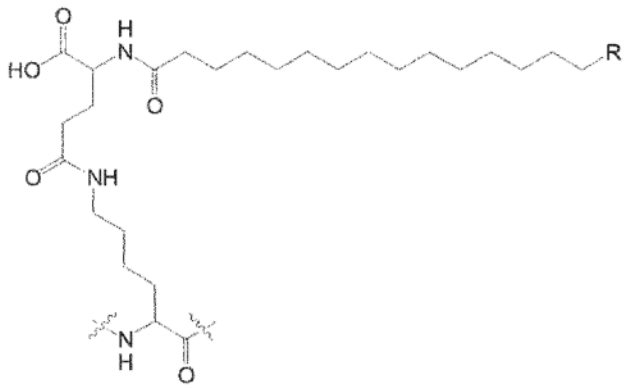
Section X.A above establishes the subject matter of claim 1 was obvious. Section X.E establishes the subject matter of claim 5 was obvious. Claim 6 was obvious for the same reasons. While claim 6 is limited to b is 18, rather than 16 to 18, this is expressly disclosed in the ’537 Publication, as discussed above. For example, the ’537 Publication Examples 5 disclose b is 18, satisfying the limitation “wherein b is 18.” EX1009, 47:4-26. This is consistent with the disclosures of the’483 Publication as well. EX1008, [0061], [0065]. Claim 6 as a whole was thus obvious. EX1002, ¶172.

Claim 6	Prior Art
b is 18	**The ’537 Publication teaches:** b is 18 Example 5  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:4-26. **The ’483 Publication teaches:** 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.” EX1008, [0061].

G. Claim 7

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

Section X.A above establishes the subject matter of claim 1 was obvious. Section X.D establishes the subject matter of claim 4 was obvious. Claim 7 was obvious for the same reasons. While claim 7 is limited to a is 1, rather than 1 to 2, this is expressly disclosed in the ’537 Publication, as discussed above. For example, the ’537 Publication Examples 4 and 5 disclose 1 is 1, satisfying the limitation “wherein a is 1.” EX1009, 47:4-26. This is consistent with the disclosures of the’483 Publication as well. EX1008, [0065]-[0066]. Claim 7 as a whole was thus obvious. EX1002, ¶173.

Claim 7	Prior Art
	The ’537 Publication teaches: a is 1 **Example 4** N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(17-Carboxyheptadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.  [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**  N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.
a is 1	EX1009, 47:4-26. **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 $_\gamma$**Glu spacer** (Z^2) via an amide linkage.” EX1008, [0065]-[0066].

H. Claim 9

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

Section X.A above establishes the subject matter of claim 1 was obvious. Section X.D establishes the subject matter of claim 4 was obvious. Claim 9 was obvious for the same reasons. While claim 9 is limited to the C-terminal amino acid as amidated as a C-terminal primary amid, rather than this amidation being optional as in claim 1, this is expressly disclosed in the ’657 and ’483 Publications. 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 as a whole was thus obvious. EX1002, ¶174.

Claim 9	Prior Art
C-terminal primary amide	**The ’657 Publication teaches:** The C-terminal amino acid is optionally amidated. “[T]he C-terminal amino acid is optionally amidated[.]” EX1007, 2:23. **The ’483 Publication teaches:** GIP/GLP-1 receptor dual agonist compounds having C-terminal primary amide. **Table 1.** **Compound No.** — **Sequence** 1 — Hy-Y-Aib-EGTFISDYSIYLEKKAAKEFVNWLLAQK-NH_2 2 — Hy-Y-Aib-EGTFTSDYSI-Aib-LDKKAQRAFVEWLLAQGPSSGAPPPS-NH_2 3 — Hy-Y-Aib-EGTFTSDYSIALDKIAQRAFVNWLVA-Aib-K-NH_2 4 — Hy-Y-Aib-EGTFISDYSIYLEKIAAKEFVNWLLAQK-NH_2 5 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 **Table 2.** **Compound No.** — **Sequence** 6 — pGlu-YAEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 7 — Hy-YGEGTFTSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 8 — Hy-Y-Aib-EGTFSSDYSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 9 — Hy-Y-Aib-EGTFTSDLSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 10 — Hy-Y-Aib-EGTFTSDSSIYLDKKAQRAFVNWLLA-Aib-K-NH_2 11 — Hy-Y-Aib-EGTFTSDYLIYLDKKAQRAFVNWLLA-Aib-K-NH_2 12 — Hy-Y-Aib-EGTFTSDYSIALDKKAQRAFVNWLLA-Aib-K-NH_2 13 — Hy-Y-Aib-EGTFTSDYSIYSDKKAQRAFVNWLLA-Aib-K-NH_2 14 — Hy-Y-Aib-EGTFTSDYSIYLEKKAQRAFVNWLLA-Aib-K-NH_2 15 — Hy-Y-Aib-EGTFTSDYSIALEKKAQRAFVNWLLA-Aib-K-NH_2 16 — Hy-Y-Aib-EGTFTSDYSIYLDSKAQRAFVNWLLA-Aib-K-NH_2 17 — Hy-Y-Aib-EGTFTSDYSIYLDEKAQRAFVNWLLA-Aib-K-NH_2 18 — Hy-Y-Aib-EGTFTSDYSIYLDSKAKRAFVNWLLA-Aib-K-NH_2 19 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQKEFVNWLLA-Aib-K-NH_2 20 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVKWLLA-Aib-K-NH_2 21 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLVA-Aib-K-NH_2 22 — Hy-Y-Aib-EGTFTSDYSIYLDKKAQRAFVNWLSA-Aib-K-NH_2 65 EX1008, 65-67 (Tables 1-2). Use of pharmaceutically acceptable salts of peptides. “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**.” EX1008, [0081]. “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." EX1008, [0084].

I. Claim 10

10. The compound of claim 1, wherein:

X_1 is Aib

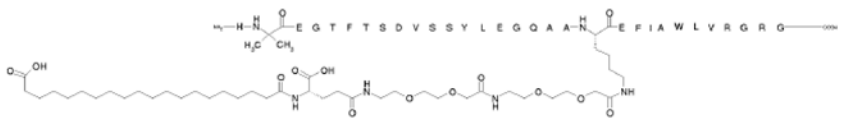
X_2 is Aib

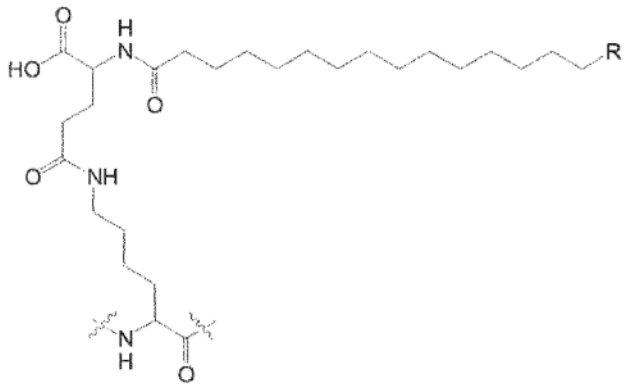
K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K sidechain with ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)$_1$-CO-(CH_2)$_{18}$-CO_2H;

X_3 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.

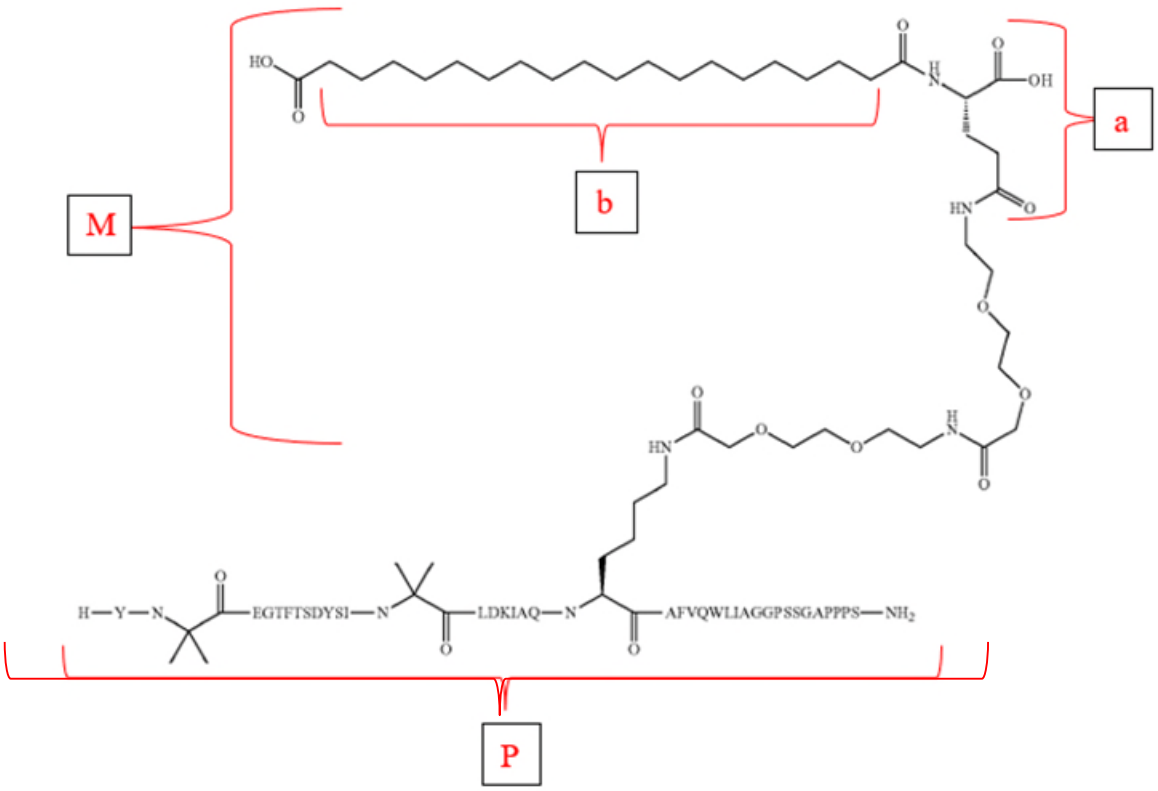
Section X.A above establishes the subject matter of claim 1wass obvious. Claim 10 was obvious for the same reasons discussed above. While claim 10 is limited to Phe^{22}, rather than 1-Nal^{22}, this is expressly disclosed for GIP/GLP-1 receptor dual agonism in both the '657 and '483 Publications, as discussed above in Section X.B. While claim 10 is limited to b is 18, rather than 10 to 20, this is expressly disclosed in the '537 Publication, as discussed above in Section X.F. While claim 10 is limited to a is 1, rather than 1 to 2, this is expressly disclosed in the '537 Publication, as discussed above in Section X.G. Claim 10 as a whole was thus obvious. EX1002, ¶175.

Claim 10	Prior Art
Claim 1, wherein X_3 is Phe A is 1 B is 18	**The '657 Publication teaches:** Phe[22]: The present invention provides a peptide comprising the sequence: Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- 15 5 10 Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-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 Xaa[2]-Xaa[3] (SEQ ID NO:1) wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated. EX1007, 2:12-25 (claimed sequence residues highlighted in green). **The '537 Publication teaches:** The claimed albumin-binding moiety conjugated to epsilon-amino group of Lys[20]. **Example 5**  N-ε[26]-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide. EX1009, 47:23-26.

	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 $_{\gamma}$**Glu spacer** (Z^2) via an amide linkage.” EX1008, [0065]-[0066]. 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.” EX1008, [0061].

J. Claim 15

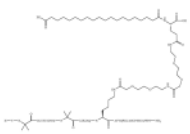
The compound of claim 1, wherein the Formula is:



Section X.A above establishes the subject matter of claim 1 was obvious. As Dr. Cornish explains, 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 $_{\gamma}$Glu (a=1). EX1002, ¶176. Claim 15 was obvious for the same reasons discussed above.

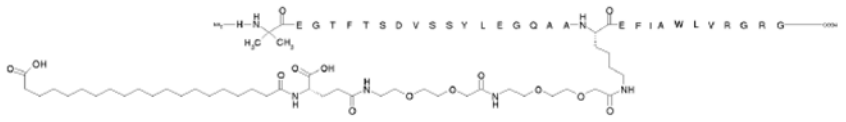
While claim 15 is limited to Phe^{22}, rather than 1-Nal^{22}, this is expressly

disclosed for GIP/GLP-1 receptor dual agonism in both the ’657 and ’483 Publications, as discussed above in Section X.B. While claim 15 is limited to b is 18, rather than 10 to 20, this is expressly disclosed in the ’537 Publication, as discussed above in Section X.F. While claim 15 is limited to a is 1, rather than 1 to 2, this is expressly disclosed in the ’537 Publication, as discussed above in Section X.G. The structure of the albumin-binding moiety in Example 5 of the ’537 Publication, including the linker and the fatty acid chain, is identical to that depicted in claim 15. EX1002, ¶176. Claim 15 as a whole was thus obvious.

Claim 15	Prior Art
	**The ’657 Publication teaches:** Phe[22]: The present invention provides a peptide comprising the sequence: Tyr-Aib-Glu-Gly-Thr-Phe-Thr-Ser-Asp-Tyr-Ser-Ile-Aib-Leu- Asp-Lys-Ile-Ala-Gln-Arg-Ala-Xaa[1]-Val-Gln-Trp-Leu-Ile-Ala- Aib-Lys-Gly-Lys-Lys-Gln-Glu-Trp-Lys-His-Gln-Ile-Thr-Gln- Xaa[2]-Xaa[3] (SEQ ID NO:1) wherein Xaa[1] at position 22 is Nal or Phe; Xaa[2] at position 43 is Cys or absent; Xaa[3] at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa[2] at position 43 or Xaa[3] at position 44 is Cys, then either or both are optionally PEGylated. EX1007, 2:12-25 (claimed sequence residues highlighted in green).

The ’537 Publication teaches:
The claimed albumin-binding moiety conjugated to epsilon-amino group of Lys^{20}.

Example 5

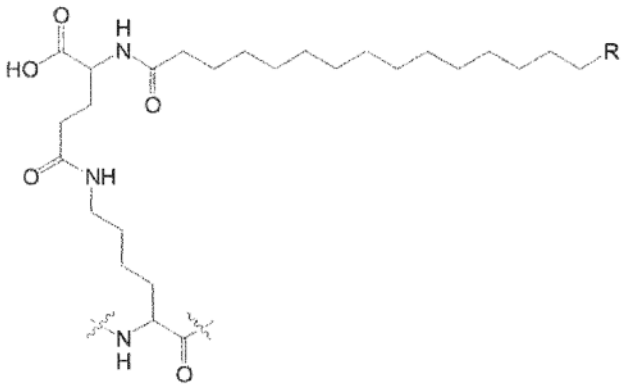


N-ε^{26}-[2-(2-[2-(2-[2-(2-[4-(19-Carboxynonadecanoylamino)-4(S)-carboxybutyrylamino]ethoxy)ethoxy]acetylamino)ethoxy]ethoxy)acetyl][Aib8,Arg34]GLP-1-(7-37)peptide.

EX1009, 47:23-26.

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 $_{\gamma}$**Glu spacer** (Z^2) via an amide linkage.” EX1008, [0065]-[0066].

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.” EX1008, [0061].

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.

Sections X.I and X.J above respectively establish the subject matter of claims 10 and 15 was obvious. The ’657 and ’483 Publications each further disclose a pharmaceutical composition comprising the compound with a pharmaceutically acceptable carrier, diluent, or excipient and that formulations and processes for preparing the same are well known in the art. EX1007, 4:26-5:21, Claims 13-14; EX1007, 25:4-9; EX1008, [0081], Claims 25-27; EX1008, [0083]-[0084], [0086]. Each of claims 12 and 16 was thus obvious as a whole. EX1002, ¶¶177-180.

Claims 12/16	Prior Art
A pharmaceutical composition comprising the compound of claim 10 [15] with a pharmaceutically acceptable carrier, diluent, or excipient.	**The '657 Publication teaches:** Formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient "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**." EX1007, 4:26-5:21; *see also* EX1007, Claim 13. **The '483 Publication teaches:** Formulating the peptide in a pharmaceutical formulation comprising a pharmaceutically acceptable carrier, diluent, or excipient. "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." 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].

Sections X.I and X.J above respectively establish the subject matter of claims 10 and 15 was obvious. The '657 and '483 Publications each further 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. 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. EX1007, 3:32-4:14 (“method for inducing weight loss”), Claims 15-19. 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.” EX1007, 25:9-20. The ’483 Publication similarly 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. EX1008, [0052], [0071], [0077]-[0078], [0085], Claims 28-36, 45-49. Each of claims 13 and 17 was thus obvious as a whole. EX1002, ¶¶181-184.

Claims 13/17	Prior Art
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].	**The '657 Publication teaches:** 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. "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…." EX1007, 3:32-4:6. "**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." EX1007, Claim 15. "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." EX1007, 25:10-12. **The '483 Publication teaches:** 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. "**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**…." EX1008, Claims 48-49. "The GIP analogue compounds employed in the context of the invention may provide an **attractive treatment option** for metabolic diseases including obesity, **diabetes mellitus** (diabetes), obesity-related disorders, and diabetes-related disorders." EX1008, [0071].

	"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. EX1008, [0078]. *See also* EX1008, [0052], [0077], [0085], Claims 29, 31, 46-47.

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.

Section X.L establishes the subject matter of claims 13 and 17 was obvious. The '657 and '483 Publications each further disclose administering simultaneously, separately, or sequentially in combination with an effective dose of one or more agents recited in claims 14 and 18.

For example, the '657 Publication teaches formulating the peptide in a pharmaceutical formulation together with "other therapeutic agents." EX1007, 4:26-5:21, Claim 14. As another example, the '483 Publication 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. EX1008, [0087]-[0090]. Each of claims 14 and 18 thus was obvious as a whole. EX1002, ¶185.

Claims 14/18	Prior Art
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.	**The '657 Publication teaches:** Co-administration with other therapeutic agents. "In a particular embodiment, the composition further comprises one or more **other therapeutic agents**." EX1007, 5:20-21; *see also* Claim 14. **The '483 Publication teaches:** Co-administration with an effective amount of metformin, sulfonylurea, or DPP-IV inhibitor. "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. EX1008, [0087]-[0088].

N. Reason to Combine and Reasonable Expectation of Success.

As explained in detail above, the prior art teaches or suggests every element of each challenged claim, and provides good reason to make the claimed compounds and use the claimed methods with a reasonable expectation of success. The prior art thus renders obvious each claim as a whole.

The '657 and '483 Publications both teach successfully making GIP analogues useful for GIP/GLP-1 receptor dual agonism, including for the treatment of diabetes and obesity. EX1007, Abstract, 2:5-10, 3:32-4:14, 11:20-15:3, 17:1-

24:1, Tables 1-2, 4-7, Claims 15-19; EX1002, ¶¶101-105, 107-109; EX1008, Abstract, [0002], [0005], [0109]-[0115], [0117]-[0119], Table 3, Figs. 1-7, Claims 28-36 & 45-49; EX1002, ¶¶111-116, 129. The ’483 Publication teaches a genus of GIP/GLP-1 receptor dual agonists that essentially encompasses the N-terminal peptide sequence of SEQ ID NO:1 in the ’657 Publication, but succeeds by truncating the peptide after position 28 or substituting the C-terminal residues with the familiar exenatide C-terminal motif. EX1002, ¶128; EX1008, [0007], [0017]; *see also* EX1002, ¶¶115-124, 147 & n.280; EX1008, [0006], [0024]-[0025]. The structure-activity relationship in the ’483 Publication indicates that applying the familiar exenatide C-terminal motif to the ’657 Publication’s sequence will make a useful GIP/GLP-1 receptor dual agonist. EX1002, ¶¶124, 139-140.

The '483 Publication further teaches acylating the peptide through conjugation to the epsilon-amino group of a lysine (including at position 20) to prolong duration of action. EX1008, [0006], [0027], [0056]-[0058], [0063]-[0066]; EX1002, ¶¶120, 126. The ’537 Publication specifically teaches conjugation of the albumin-binding moiety (([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)-CO-(CH_2)$_{16\text{-}18}$-CO_2H)) to the epsilon-amino group of the lysine amino acid residue at position 20 prolongs the duration of action of the agonist, thereby achieving once-weekly dosing. EX1009, Examples 4-5; EX1002, ¶¶130-133; EX1010, 1:21-23. Based on the known structure-activity-relationships for GIP/GLP-1 receptor dual

agonism and the known and successful use of the claimed albumin-binding moiety to impart protracted duration of action, a skilled artisan had good reason with a reasonable expectation of success to conjugate the albumin-binding moiety to Lys^{20} of the peptide. EX1002, ¶¶135, 98, 165; *see also* Section VIII.A; EX1075, Abstract, 2:21-25, 19:28-37, 25:25-26:6, 36:7-10, 38:6-10, 49-51 (Table 1), 58 (Table 4).

A POSA had good reason to look to the combined teachings of the ’657, ’483, and ’537 Publications to make a GIP/GLP-1 receptor dual agonist. All three publications are directed to making and using synthetic incretin peptides that are useful for GLP-1 receptor agonism, including for the treatment of type-2 diabetes and obesity. EX1002, ¶¶101, 111-12, 130-131; EX1007, Abstract, 1:8-23, 2:5-10; EX1008, Abstract, [0002]-[0004]; EX1009, Abstract. Both the ’657 and ’483 Publications describe how to make and use GIP analogues that are GIP/GLP-1 receptor dual agonists. They elucidate a structure-activity relationship for GIP/GLP-1 receptor dual agonism that is consistent with both publications. EX1002, ¶147 n.280 (’483 Publication SAR encompasses and is consistent with SEQ ID NO:1 in the ’657 Publication); *see also* EX1002, ¶¶115-125, 148-158 (discussing SAR). A POSA thus had good reason to combine the ’657 and ’483 Publications to understand and apply their teachings about the SAR to make new GIP/GLP-1 receptor dual agonists. EX1002, ¶¶144-145. Indeed, a POSA had good

reason to combine the ’657 and ’483 Publications to obtain an effective GIP/GLP-1 receptor dual agonist having favorable metabolic stability and immunogenicity profile. EX1002, ¶¶135-138, 150-152, 154; *see also* EX1002, ¶¶94-98; EX1069, 4-8; EX1070, Abstract; EX1071, Abstract, 1700-01; EX1072, Abstract, 155-57; EX1073, Abstract, 17-21, Table 2; EX1074, Abstract, 75-79, 82-84, Table 1.

The ’483 Publication expressly suggests conjugating the dual agonist compounds at Lys^{20} to an albumin-binding moiety to achieve protracted duration of action. EX1008, [0006], [0064]-[0066], [0056]-[0058], [0060]-[0061]; EX1002, ¶¶122, 126. A POSA had good reason to look to the ’537 Publication for the Lys^{20}-conjugated albumin-binding moiety that was used to achieve once-weekly dosing in semaglutide to provide the same benefit (protracted duration of action) to the dual agonist peptides rendered obvious by the ’657 and ’483 Publications. EX1002, ¶¶114, 135, 164-165; EX1010, 1:21-23; EX1009, 1:5-34, 2:1-13, 3:8-4:8, 6:6-21, Examples 4-5. The dual agonism SAR demonstrated in the ’483 Publication indicated that using Lys^{20} for conjugation was very consistent with effective GIP/GLP-1 receptor dual agonism. EX1002, ¶¶115, 122, 126. As Dr. Cornish explains, both the peptide synthesis and chemical conjugation at issue were very straightforward and well-within the skill of a POSA at the time. EX1002, ¶135. A POSA therefore had good reason to make and use compounds falling within the scope of the challenged claims with a reasonable expectation of

success. *Id.*

Among other things, as explained by Dr. Cornish, it was obvious to make and use compounds falling within the scope of the challenged claims because:

- A POSA would have recognized that these compounds have very close structural similarity to prior art dual GIP/GLP-1 receptor agonists and were likely to share a similar utility with prior art dual GIP/GLP-1 receptor agonists (EX1002, ¶¶137-138);
- The prior art disclosed a suitably operative process for making these compounds (EX1002, ¶137);
- These compounds are consistent with the known structure-activity relationship ("SAR") for GIP/GLP-1 dual agonism expected to have GIP/GLP-1 dual agonism properties (EX1002, ¶137);
- 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 (EX1002, ¶137);
- 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 (EX1002, ¶137);
- A POSA would have recognized from the prior art dual agonism SAR that

SEQ ID NO:1 of the ’657 Publication was a lead compound that 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 (EX1002, ¶139);

- A POSA would have recognized from the prior art dual agonism SAR that SEQ ID NO:1 of the ’657 Publication desirably would have been modified or even improved by conjugating the peptide at the epsilon amino of a Lys^{20} to a prior art albumin-binding moiety already used to improve the *in vivo* half-life of the GLP-1 agonist semaglutide, which achieved a dosing frequency of once-weekly (EX1002, ¶139).

As Dr. Cornish further explains, a compound within the scope of the claim 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 Lys^{20} as disclosed in the ’483 Publication, and with the Lys^{20}-conjugated albumin-binding moiety 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. EX1002, ¶140. This combination similarly:

- substitutes one known element for another to obtain predictable results;
- uses a known technique (albumin-binding moiety conjugation at the epsilon amino of Lys^{20}) to improve a similar product in the same way to yield

predictable results; and

- was obvious to try from among a finite number of identified, predictable solutions for which there was a reasonable expectation of success.

EX1002, ¶140. Ultimately, all challenged claims were obvious over the combined teachings of the '657, '483, and '537 Publications. *KSR*, 550 U.S. at 416-17.

XI. SECONDARY CONSIDERATIONS

No secondary considerations of non-obviousness were cited as a basis for allowance during prosecution. *See* Section V.B above. Moreover, none are apparent from the specification. EX1002, ¶¶187-188. The challenged patent repeatedly asserts that GIP/GLP-1 receptor dual agonists are more effective than GLP-1 receptor mono-agonists alone, but this is not a secondary consideration of non-obviousness. As explained in Section VIII.A-C above, this effect was known and expected. EX1002, ¶¶189-190. This was precisely why POSAs were making dual agonists, identifying their SAR, identifying ways to stabilize them against proteolytic degradation without causing undue immunogenicity (*e.g.*, appending the exenatide C-terminal motif), and looking for ways to prolong their duration of action (*e.g.*, employing the albumin-binding moiety that achieved once-weekly dosing for semaglutide). As Dr. Cornish explains, 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. EX1002, ¶¶189-190.

The ’780 Patent does not demonstrate the claimed peptides have superior efficacy as compared to prior art GIP/GLP-1 receptor dual agonists, much less as compared to the closest prior art. EX1002, ¶¶190-191. Instead of comparing to dual agonists, the activity tables in the challenged patent provide direct comparisons to control. EX1001, Tables 1-15; EX1002, ¶192. Even if a comparison could be extrapolated to semaglutide in some experiments, semaglutide is ***not*** a dual agonist and is ***not the closest prior art***. EX1002, ¶192. All dual agonists tested in the challenged patent appear to work generally similarly to one another, successfully binding both receptors with high affinity, activating them with nanomolar potency, stimulating insulin secretion, and reducing blood glucose, cholesterol, and triglycerides as compared to control. EX1002, ¶192. Though the specification touts its dual agonists as “balanced” (EX1001, 6:36-43), it never demonstrates their properties are absent in the prior art dual agonists (they are not). EX1002, ¶190 n.387; s*ee* Section VIII.A-C above. The challenged patent thus does not demonstrate any difference compared to the closest prior art, certainly not any difference in kind. EX1002, ¶¶191-192.

Nor does the challenged patent demonstrate that once-weekly dosing was an unexpected result. As Dr. Cornish explains, it was not unexpected to achieve once-weekly dosing using the prior art albumin-binding moiety that is claimed by the ’780 patent here, which successfully achieved once-weekly dosing with

semaglutide. EX1002, ¶194. Low immunogenicity from using exenatide's C-terminal motif instead of the artificial Aib residues at position 29 and the artificial C-terminal motif in SEQ ID NO:1 of the '657 Publication was both expected and predictable, not an unexpected result. EX1002, ¶195. The data in the challenged patent thus fails to demonstrate any unexpected result, much less a difference in kind, as compared to the closest prior art. EX1002, ¶196.

XII. CONCLUSION

Claims 1-7, 9-10, 12-18 are unpatentable. Empower respectfully requests institution of IPR and cancelation of the challenged claims.

Respectfully submitted,

Dated: 22 May 2025

/ Jad Mills /
Jad Mills, Reg. No. 63,344
Counsel for Empower Clinic Services L.L.C.
(d/b/a Empower Pharmacy)

PAYMENT OF FEES UNDER 37 C.F.R. §§42.15(A) AND 42.103

The required fees have been paid. If any additional fees are due at any time during this proceeding, the Office is authorized to charge such fees to Deposit Account No. 23-2415.

CERTIFICATION UNDER 37 C.F.R. §42.24(D)

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Petition complies with the type-volume limitation of 37 C.F.R. §42.24(a). The word count application of the word processing program used to prepare this Petition indicates that the Petition contains 12,219 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(a).

Respectfully submitted,

Dated: 22 May 2025

/ Jad Mills /
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Counsel for Empower Clinic Services L.L.C.
(d/b/a Empower Pharmacy)

LIST OF EXHIBITS

Exhibit No	Description
1001	U.S. Patent No. 9,474,780.
1002	Declaration of Dr. Virginia W. Cornish, Ph.D.
1003	*Curriculum Vitae* 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	Gregg B. Fields, *Introduction to Peptide Synthesis*, 26 CURRENT PROTOCOLS IN PROTEIN SCI., 18.1.1-18.1.9 (2002).
1012	U.S. Patent Publication No. 2015/0299281 A1.
1013	SAXENDA (liraglutide) injection drug label (Dec. 2014) ("SAXENDA") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2014/206321Orig1s000lbl.pdf.
1014	David L. Nelson & Michael M. Cox, LEHNINGER PRINCIPLES OF BIOCHEMISTRY Chapters 4-5, 7 (3rd ed. 2000).
1015	Deborah L. Segaloff & Mario Ascoli, *Chapter 9: Internalization of Peptide Hormones and Hormone Receptors, in* HORMONES AND THEIR ACTIONS, PART I 133-149 (B.A. Cooke et al. eds., 1988).
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Exhibit No	Description
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1054	BYETTA (exenatide) injection drug label (Apr. 2005) ("BYETTA") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/label/2005/021773lbl.pdf.
1055	TRULICITY (dulaglutide) injection drug label (Sept. 2014) ("TRULICITY") *available at* https://www.accessdata.fda.gov/drugsatfda_docs/nda/2014/125469Orig1s000Lbl.pdf.
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Exhibit No	Description
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CERTIFICATE OF SERVICE

I certify that today this petition and Exhibits EX1001-EX1075 were served by *Priority Mail Express Delivery* on the Patent Owner's correspondence address of record for this patent as follows:

25885 - Eli Lilly & Company
Patent Division
P.O Box 6288
Indianapolis, IN 46206-6288
United States

All statements in this certificate of service made of my own knowledge are true and all statements made on information and belief are believed to be true. I acknowledge that willful false statements and the like are punishable by fine or imprisonment, or both (18 U.S.C. §1001) and may jeopardize the validity of this proceeding.

Respectfully submitted,

Dated: 22 May 2025

/ Christopher F. Kielman /
Christopher F. Kielman