A summary of Alsina-Fernandez, DiMarchi, and Lau is also provided in Dr. Zhou's declaration that provides additional background information. *See* EX1084 at ¶¶91-101 (Alsina-Fernandez), 102-106 (DiMarchi) and 107-111 (Lau).

## X. HOW THE CLAIMS ARE UNPATENTABLE UNDER 37 C.F.R. § 42.104(b)(4)

### A. Level of Skill in the Art

In view of the subject matter of the '780 Patent, a POSA at the time of the invention would typically have a Ph.D. in chemistry, organic chemistry, bioorganic chemistry, protein engineering or a related field. *See* EX1084 at ¶¶54-56. Skilled artisans also could include individuals with a master's degree in one of these fields plus two-to-five years of experience in peptide design. *Id*. This individual may have worked in consultation with a team including, *e.g.*, a pharmaceutical chemist or a pharmacist familiar with formulating peptides for administration. *Id*. This individual may have consulted with a physician with experience administering peptides for the treatment of diabetes or obesity. *Id*.

### B. Alsina-Fernandez in view of DiMarchi and Lau renders obvious claims 1-2, 4-7, 9-10, and 12-18

Based on the understanding in the field prior to 2015, a POSA was motivated to develop GLP-1/GIP co-agonist compounds for the treatment of diabetes mellitus, as well as weight loss, as the dosing of selective GLP-1 agonist compounds was

limited by the nausea and vomiting associated with their administration, preventing these compounds from reaching their full efficacy for glycemic control and weight loss. EX1084 at ¶113. The prior art (Alsina-Fernandez, DiMarchi, and Lau) provided guidance in the form of well-known structural substitutions and modifications that represented rational design strategies related to the development of co-agonists of GIP/GLP-1, particularly in view of a POSA's well-established motivations to (1) solve/mitigate the issues associated with nausea and vomiting caused by selective GLP-1 agonist compounds; (2) minimize any potential immunogenicity associated with regular administration of the GLP-1/GIP co-agonist compounds; and (3) provide for a longer half-life and duration of effect, allowing for less frequent injections of the medication (e.g., once-weekly dosing), as compared to the dosing frequency required with shorter half-life compounds (e.g., once daily dosing). *Id*.

A POSA would have been motivated to use Alsina-Fernandez Example 2 as a lead compound, and modify it in view of the teachings of DiMarchi and Lau to achieve these desired attributes as explained herein based on the declaration provided by Dr. Zhou. Given the well-studied mechanisms of action for GIP and GLP-1 agonists, discussed in the Background of the Technology, a POSA would have had a reasonable expectation of success of combining Alsina-Fernadez, DiMarchi, and Lau as discussed below. *See supra*, Section VIII. Finally, neither

Petitioner nor Dr. Zhou are aware of any surprising and unexpected results, or any other secondary considerations, that could overcome the obviousness of claims 1-2, 4-7, 9-10, and 12-18 in view of the ground of rejection provided in this Petition. *See* EX1084 at ¶114.

**1. Claim 1**

**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.**

***1. Known Problems with GLP-1 Compounds Prior to 2015, and Alsina-Fernandez's Promising Prior Art GIP/GLP-1 Co-Agonist***

By January 2015, it was well known in the art that GLP-1 agonist compounds and products were being used and developed for not only the treatment of type 2 diabetes mellitus ("T2D"), but also for weight loss. Specifically, by December 2014,

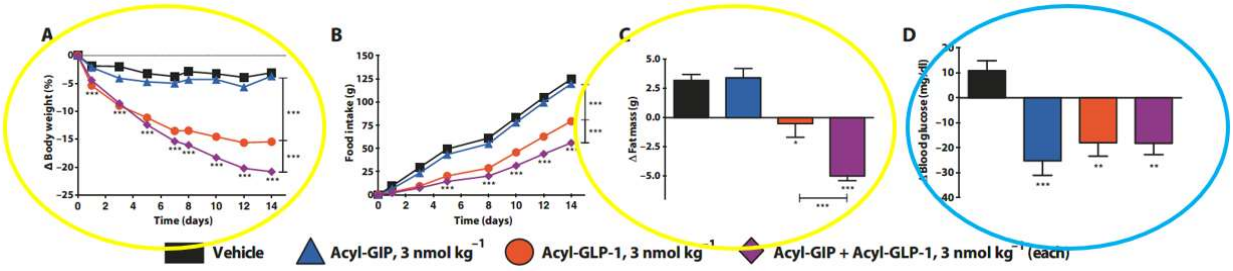
exenatide (a GLP-1 receptor agonist) and liraglutide (a GLP-1 receptor agonist) had been approved by the FDA for both the treatment of diabetes (as the Victoza® product) and for chronic weight management (as the Saxenda® product). EX1084 at ¶117; *see, e.g.*, EX1050 and EX1013. It was well established that obesity had become a serious public health issue due to its prevalence and common association with high rates of morbidity and mortality, driving significant interest in the development of treatments specific to obesity beyond known measures at the time, such as bariatric surgery. EX1084 at ¶117; *see* EX1083. And the field had also begun to recognize GLP-1 receptor agonists as a new and promising treatment option for obesity. EX1084 at ¶113; EX1083 at Abstract ("with the GLP-1 analogues combining a moderate weight loss with beneficial effects on metabolic and cardiovascular risk factors, it seems that we are on the right track for future treatment of obesity"). But, it was also known in the field that the nausea and vomiting associated with GLP-1 agonists limited use of the compounds. EX1084 at ¶113; *see, e.g.*, EX1061 at 11-12 (discussing "dose-limiting nausea complications that restrict current selective GLP-1R agonists"). Indeed, by the '780 Patent's own admission, "[d]osing of GLP-1 analogues has been found to be limited by adverse effects, such as **nausea and vomiting**, and as a consequence dosing most often cannot reach full potential efficacy for glycemic control and weight loss." EX1001 at 1:37-40

(emphasis added)[8]. With this known problem in mind, a POSA would have looked for strategies to solve or mitigate nausea. EX1084 at ¶117.

Finan, published in 2013, establishes that co-agonists of GLP-1 and GIP can enhance weight loss efficacy, while at the same time lessening nausea. EX1084 at ¶118; EX1061 at 11-12. Finan explains that co-agonists of GLP-1 and GIP provide greater metabolic efficacy than selective GLP-1 agonists, but without the gastrointestinal discomfort (e.g., nausea and vomiting) associated with selective GLP-1 agonists. EX1084 at ¶119. Finan further explains that the addition of GIP agonism to GLP-1 agonists strengthens the inherent efficacy and therapeutic index of GLP-1 agonists, meaning results can be achieved using lower doses (more closely approximating physiologic levels), and circumventing the dose-limiting nausea complications typically associated with GLP-1 agonists. EX1084 at ¶120; EX1061 at 12.

As shown in the annotated version of Finan's Figure 1 below, co-administration of GLP-1 and GIP peptides provided enhanced weight and fat loss (yellow circles), while maintaining blood glucose lowering efficacy similar to a GLP-1 agonist (blue circle) in diet-induced obese (DIO) mice. EX1084 at ¶121; EX1061 at 3, Fig. 1A-1D.

[8] All emphasis added unless otherwise noted.




Based on the disclosure of Finan, as of 2013, a POSA would have been motivated to investigate co-GLP-1/GIP agonist compounds as an alternative to selective GLP-1 receptor agonists, as co-GLP-1/GIP agonist compounds were shown to maintain, and in some instances enhance, the glycemic control and weight loss properties of GLP-1 compounds, while circumventing the nausea typically associated with GLP-1 administration. EX1084 at ¶122.

In view of this, a POSA would have looked to Alsina-Fernandez as a primary source of guidance, as Alsina-Fernandez discloses GIP/GLP-1 co-agonist peptide sequences useful for treating diabetes and/or reducing body weight. EX1084 at ¶123; EX1007 at Abstract, 2:12-25, 5:24-27, Claims 1-12. Alsina-Fernandez discloses that its GIP/GLP-1 co-agonist peptide sequence is both potent and efficacious for reducing body weight and reducing glucose sensitivity, explaining that dual agonism uses the glucose-lowering effects of GLP-1 to better harness the insulin-secretion effects of GIP. EX1084 at ¶123; EX1007 at 2:5-10, 11:20-27, 1:8-21. Thus, Alsina-Fernandez provides teachings regarding co-GLP-1/GIP agonists, and in fact notes

that the co-agonists described therein address some of the very same issues that Finan discusses and attempts to address (i.e., co-agonism of GIP/GLP-1, with selectivity over glucagon, providing an effective treatment for reducing body weight). EX1084 at ¶123; EX1007 at 2:5-10.

In view of these teachings, a POSA would have looked at Alsina-Fernandez as a lead reference in the development of a co-GLP-1/GIP agonist. EX1084 at ¶124; Based on the disclosure of Alsina-Fernandez, a POSA had good reason to make and evaluate structurally similar peptide sequences likely to share the GIP/GLP-1 receptor co-agonist functionality. *Id*. In particular (and as explained below), while co-agonists of GIP/GLP-1 were disclosed in a number of references (e.g., Alsina-Fernandez, DiMarchi, Finan, etc.) a POSA was motivated to look to Example 2 of Alsina-Fernandez, as a lead compound for further development and optimization because of its promising GIP/GLP-1 dual agonism properties, and selectivity over the glucagon receptor. *Id*.; *Otsuka Pharm. Co. v. Sandoz, Inc*., 678 F.3d 1280,1291 (Fed. Cir. 2012) ("A lead compound, as we have explained, is a compound in the prior art that would be most promising to modify in order to improve upon its...activity and obtain a compound with better activity.")(internal quotes omitted); *Altana Pharma AG v. Teva Pharmaceuticals USA, Inc*., 566 F.3d 999, 1008–09 (Fed. Cir. 2009) (the lead compound can be one of a group of promising compound, and the prior art need not "point to only a single lead compound for

further development efforts, that restrictive view of the lead compound test would present a rigid test similar to the teaching-suggestion-motivation test that the Supreme Court explicitly rejected in KSR").

Alsina-Fernandez focuses on a primary amino acid sequence with three variable amino acids (noted as $Xaa^{1-3}$):

> 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.

EX1007 at 2:12-25.

For ease of viewing, SEQ ID NO: 1 of Alsina-Fernandez is reproduced below in linear form:

Y-Aib-E-G-T-F-T-S-D-Y-S-I-Aib-L-D-K-I-A-Q-R-A-$Xaa^1$-V-Q-W-L-I-A-Aib-K-G-K-K-Q-E-W-K-H-Q-I-T-Q-$Xaa^2$-$Xaa^3$

$Xaa^1$ = naphthylalanine (Nal) or Phenylalanine (Phe or "F")

$Xaa^2$= cysteine (Cys or "C") or absent

$Xaa^3$= cysteine (Cys or "C") or absent

EX1084 at ¶125.

In addition, Alsina-Fernandez provides *in vitro* and *in vivo* data indicating the peptides have utility as a GIP/GLP-1 co-agonist, including for glycemic control and weight loss. EX1084 at ¶126. First, Alsina-Fernandez reports GIP and GLP-1 $K_i$ values for the peptide approaching low picomolar concentrations (*see* Example 1 and Example 2 compounds), regardless of whether the amino acid residue at position 22 is Phe (F) or 1-Nal. *Id*.; EX1007 at 11:29-15:4. Specifically, the $K_i$ values reported in Tables 1 and 2 represent receptor binding affinities, and correlate to the $IC_{50}$ concentration for agonist activity of the GIP and GLP-1 receptors, respectively, reflecting the concentration of the compound required to provide agonist activity at 50% of the receptors. EX1084 at ¶126. The lower the Ki value, the more potent the binding to the GIP and GLP-1 receptors. *Id*. Consequently, a POSA would look to the values in Tables 1 and 2 for the compounds with the lowest Ki values, as that would be indicative of the most potent binding/agonist activity at the GIP and GLP-1 receptors. *Id*.

Provided below are annotated versions of Tables 1 (GIP receptor binding affinities) and 2 (GLP-1 receptor binding affinities) of Alsina-Fernandez:

Table 1

| Example | Ki |
|---|---|
| 1 | 0.044 nM |
| 2 | 0.023 nM |
| 3 | 9.79 nM |
| 4 | 8.23 nM |
| 5 | 9.22 nM |

Table 2

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

EX1084 at ¶127; EX1007 at 13:6-9, 14:32-15:3.

As highlighted in Table 1 and Table 2, the compound of Example 2 demonstrated the lowest Ki value for both GIP receptor binding (Table 1) and GLP-1 receptor binding (Table 2). EX1084 at ¶128. Consequently, a POSA would know that the compound of Example 2 provides the most potent binding of the GIP and GLP-1 receptors. *Id*.

Additionally, Alsina-Fernandez also reports Ki values for binding to the glucagon receptor (Gluc-R) in Table 3. EX1084 at ¶129; EX1007 at 16:22-24. In the context of co-GIP/GLP-1 agonists that are designed to provide glycemic control (e.g., by lowering blood sugar concentration), binding to the glucagon receptor is considered undesirable, Alsina-Fernandez explains that glucagon receptor binding triggers increased blood glucose levels, and "is undesirable in a diabetic setting." *Id*.; EX1007 at 1:16-17. Thus, a POSA understands that a higher Ki value (lower binding affinity) for the glucagon receptor would be desirable, as that would

minimize the release of blood glucose associated with stimulation of the glucagon receptor. EX1084 at ¶129.

Provided below is an annotated version of Table 3 (glucagon receptor binding affinities) of Alsina-Fernandez:

Table 3

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

EX1084 at ¶130; EX1007 at 16:22-24.

As highlighted in Table 3 above, the compound of Example 2 demonstrated the highest Ki value (along with the compound of Example 1) for glucagon receptor binding affinity, representing the weakest affinity for the glucagon receptor. EX1084 at ¶130. Consequently, a POSA would have known that the compound of Example 2 represents the weakest binding of the glucagon receptor, which was preferred, as binding to the glucagon receptor was undesirable (due to increased blood glucose levels triggered by stimulation of the glucagon receptor). *Id*.

Based on the data reported in the Examples, particularly in Tables 1-3, Alsina-Fernandez teaches that the compound of Example 2 had the most potent binding affinity for the GIP and GLP-1 receptors, and the weakest binding affinity for the

glucagon receptor. EX1084 at ¶132. While Example 1 demonstrated a binding affinity for GIP and GLP-1 that was better than Examples 3-5, the binding affinities for Example 2 were better (0.023 nm GIP receptor Ki for Example 2 vs. 0.044 nm GIP receptor Ki for Example 1; 0.059 nm GLP-1 receptor Ki for Example 2 vs. 0.096 nm GLP-1 receptor Ki for Example 1). EX1084 at ¶132. Additionally, it's well-known that 1-Nal (naphthylalanine, the amino acid present at position 22 of Example 1) is a non-natural amino acid with a large aromatic side chain (i.e., naphthalene), markedly increasing the potential for immunogenicity against the peptide of Example 1. *Id*. The combination of these factors would have led a POSA to focus on Example 2 as the lead co-GIP/GLP-1 agonist for further development and research. *Id*.

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

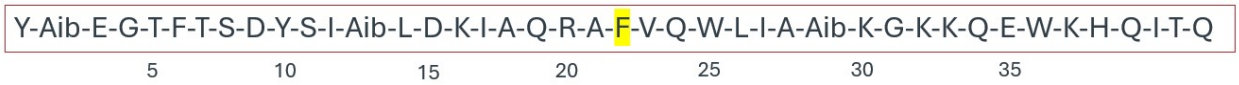
EXAMPLE 2

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

EX1084 at ¶133; EX1007 at 8:15-22.

As can be seen above, the compound of Example 2 includes Phe ("F") at position 22, and $Xaa^2$ and $Xaa^3$ are absent. EX1084 at ¶134. For ease of viewing, the

sequence of Example 2 in linear form is provided below, with the Phe residue at position 22 highlighted:




*Id*.

Further, it is noted that Alsina-Fernandez also reports that the compounds may include Cys residues at positions 43 and 44, and the compounds may also be PEGylated at the Cys43 and Cys44 residues. EX1084 at ¶135; EX1007 at 2:12-25. However, as shown in Tables 1-3 above, the compounds with PEGylated Cys residues at positions 43 and 44 (i.e., the compounds of Examples 3, 4, and 5) had lower binding affinities for the GIP and GLP-1 receptors (an ~100-400 fold lower binding affinity, depending on the peptide), and a higher binding affinity for the glucagon receptor, as compared to the compound of Example 2 (~3-fold higher binding affinity). *Id*.; EX1007 at 13:6-9, 14:32-15:3, and 16:22-24. This additional data would further motivate a POSA to focus on the compound of Example 2 as the lead candidate. EX1084 at ¶135.

In addition to these PEGylated compounds providing less advantageous binding affinities for the GIP and GLP-1 receptors (*see* Table 1 and Table 2, respectively) and glucagon receptor (*see* Table 3), a POSA was motivated to avoid PEGylated compounds based on the risk of potential immunogenicity. EX1084 at ¶136. Specifically, Alsina-Fernandez was filed in March 2011 (claiming priority to

US Prov. Pat. App. No. 61/317,850 filed March 26, 2010). Subsequently, in 2012, Garay et al. reported that, in contrast to the common thinking that PEG is non-immunogenic and non-antigenic (as was generally the thinking in the art at the time Alsina-Fernandez was filed), up to 25% of healthy blood donors (*i.e.* donors with no indication of being previously treated with a PEGylated drug), and up to 89% of patients treated with a PEGylated drug, were shown to have anti-PEG antibodies that can elicit response to PEGylated drugs or compounds. EX1084 at ¶123; EX1022 at Abstract, 1320. The response elicited by these PEG antibodies can result in decreased therapeutic efficacy and reduced tolerance to PEGylated drug compounds. *Id*. Further, avoiding potential immunogenicity is particularly important for compounds intended to be administered chronically and with repeated dosing (e.g., weekly), as opposed to acute, single, or infrequent administration. Whereas some immunogenicity might be acceptable to treat an acute condition because the peptide is only administered a small number of times, patients receiving the GIP/GLP-1 co-agonist would likely expect to be taking the compound regularly for long periods of time (perhaps the rest of their life). *Id*.

Consequently, even though Alsina-Fernandez discussed the use of PEGylated peptide compounds in Examples 3, 4, and 5, the risk of potential immunogenicity associated with the PEG further motivated a POSA to focus on the peptide of

Example 2, which nonetheless provided the most desirable binding profile for the GIP, GLP-1, and glucagon receptors. EX1084 at ¶137.

Based on the disclosures of Alsina-Fernandez, a POSA would have looked to the peptide of Example 2 as a lead compound for further development and optimization because of its most promising GIP/GLP-1 co-agonist properties (and high degree of selectivity over the glucagon receptor) and the likelihood that this compound would be favorably improved through further modification. EX1084 at ¶138.

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

In view of the teachings of Alsina-Fernandez, a POSA would have been motivated to look for guidance on strategies to improve the efficacy of the co-GIP/GLP-1 agonists described in Alsina-Fernandez. EX1084 at ¶139. In this regard, Alsina-Fernandez itself cites one reference, DiMarchi, as previously describing co-GIP/GLP-1 agonists:

> Certain glucagon analogs have been described as exhibiting both GIP and GLP-1 activity in WO 2010/011439 [DiMarchi].

EX1007 at 1:27-29. Consequently, based on this statement in Alsina-Fernandez, a POSA would have looked to DiMarchi for additional guidance on co-GIP/GLP-1 agonist compounds and strategies. EX1084 at ¶139.

DiMarchi teaches strategies for enhancing GIP and/or GLP-1 receptor activity. EX1084 at ¶140. Significantly, DiMarchi discloses that the incorporation of a glycine (G) at position 29 and attachment of the GPSSGAPPPS tail to the glycine residue at position 29 enhances GLP-1 receptor potency. *Id*.; EX1017 at 5:7-11. DiMarchi also provides specific guidance that incorporating a glycine (G) residue at position 29, and connecting the GPSSGAPPPS tail to the glycine at position 29 resulted in ***four times*** the GLP-1 receptor binding potency, as compared to attaching the GPSSGAPPPS extension to the threonine present in the native glucagon peptide. EX1084 at ¶141; EX1017 at 55:10-17.

Additionally, as discussed previously, the GGPSSGAPPPS motif had been successfully appended to DPP-IV-resistant GLP-1 to improve its potency and metabolic stability without inducing undue immunogenicity. EX1084 at ¶142; EX1070 at Abstract; EX1071 at 1700-1701, Abstract. The C-terminal motif GGPSSGAPPPS found in the FDA-approved GLP-1 receptor agonist exenatide was known to be associated with reduced clearance, improvement in half-life, and less susceptibility to undesirable DPP-IV cleavage, as demonstrated by a prolonged half-life of 2.4 hours. EX1054 at 3 (reporting a terminal half-life of exenatide of 2.4 hours); EX1076 at 4013 ("GLP-1 has a very short half-life of ~2 min"). The C-terminal motif GGPSSGAPPPS in exenatide also did not trigger strong or adverse immunogenicity, as evidenced by the low titer anti-exenatide antibodies reported for

Byetta® and Bydureon®. EX1084 at ¶142; s*ee* EX1053 at 9 ("...452 BYDUREON-treated patients (49%) had low titer antibodies (≤125) to exenatide at any time during the trials and 405 BYDUREON-treated patients (45%) had low titer antibodies to exenatide at study endpoint (24-30 weeks). The level of glycemic control in these patients was generally comparable to that observed in the 379 BYDUREON-treated patients (43%) without antibody titers."); *see also* EX1054 at 14 ("In the 30-week controlled trials 38% of patients had low titer anti-exenatide antibodies at 30 weeks. For this group, the level of glycemic control (HbA1c) was generally comparable to that observed in those without antibody titers.").

Additionally, a POSA would have recognized that the compound of Example 2 of Alsina-Fernandez unnecessarily employs a non-natural Aib residue at position 29, and also employs a long C-terminal motif that does not appear in any of the natural ligands or the FDA-approved therapeutic ligands. EX1084 at ¶143. It is well-established that the inclusion of non-natural amino acids increased the likelihood of immunogenicity. *Id*. Consequently, a POSA would have been motivated to replace the unnatural C-terminal residues 29-39 of the Example 2 compound of Alsina-Fernandez with exenatide's natural C-terminal GGPSSGAPPPS motif. *Id*. A POSA would have recognized that this prior art substitution would avoid unnecessary use of the non-natural (and potentially immunogenicity-inducing) Aib at position 29 by employing the Gly found naturally in endogenous and synthetic FDA-approved

GLP-1 receptor agonists exenatide and liraglutide, as Gly at position 29 was known to elicit low-titer anti-drug antibodies consistent with therapeutic efficacy. *Id*.; *see* EX1009 at 61:1-62:37, (Example 4, providing endogenous sequence for 31-residue version of GLP-1 with G at position 29), 3:25-28 (defining GLP-1), 4:4-16 (invoking 39-residue sequence of Exendin-4); EX1053 at 9; EX1054 at 1-2, 14; EX1070 at Abstract (exenatide safety); EX1071 at Abstract, 1700-1701 (low frequency and magnitude antibody formation for liraglutide). Accordingly, a POSA would have reasonably expected reduced immunogenicity as compared to the sequence of Example 2 of Alsina-Fernandez, which would have provided a POSA with an additional reason to apply the prior art exenatide C-terminal motif to the co-GIP/GLP-1 agonist disclosed in Alsina-Fernandez. EX1084 at ¶144; EX1053 at 9; EX1054 at 14.

In addition, Alsina-Fernandez recognized the goal of avoiding undesirable protease cleavage. It references its use of Aib residues at position 2 and 13, which were known to prevent DPP-IV-catalyzed and activity-defeating peptide cleavage, and teaches SEQ ID NO:1 is less susceptible to rapid metabolic deactivation by DPP-IV. EX1084 at ¶144; EX1007 at 5:22-23. C-terminal substitution of residues 29-39 with exenatide's C-terminal GGPSSGAPPPS motif is thus not only consistent with the purposes disclosed in DiMarchi, but also is consistent with the goals of Alsina-Fernandez. *Id*.

DiMarchi discloses more than 260 exemplary peptide sequences, of which the majority incorporated the GPSSGAPPPS tail, as described in the specification of DiMarchi, so this was clearly a preferred/prominent design strategy in DiMarchi. EX1017 at Sequence Listing for SEQ ID NOS. -262. Further, DiMarchi states that "[e]nhanced activity at the GLP-1 receptor is provided by replacing the carboxylic acid of the C-terminal amino acid with a charge-neutral group, such as an amide or ester," suggesting to a POSA that the terminal -$NH_2$ amide group attached to the terminal serine would further enhance GLP-1 receptor activity. EX1084 at ¶145; EX1017 at 33:20-21. Indeed, Finan, which published in 2013, several years after both Alsina-Fernandez (filed in 2011) and DiMarchi (filed in 2009), includes a number of exemplary peptides, the majority of which include the GPSSGAPPPS-$NH_2$ exenatide C-terminal tail, suggesting this was a continuing design strategy/motivation in the years following Alsina-Fernandez and DiMarchi. EX1084 at ¶145; EX1061 at Supplemental Figure 1. Researchers in this field would have been keenly aware of such peptide designs leading up to the filing of the '780 Patent in 2015. EX1084 at ¶145.

Based on all of these factors, a POSA would have been motivated to replace the unnatural C-terminal residues 29-39 of Example 2 of Alsina-Fernandez with exenatide's natural C-terminal GGPSSGAPPPS motif and terminal amide group (-$NH_2$) taught by DiMarchi. EX1084 at ¶146. Given the prominence of the use of the

C-terminal GPSSGAPPPS tail across numerous different peptides in DiMarchi, as well as the majority of the exemplary peptides in Finan, a POSA would have reasonably expected that the C-terminal GPSSGAPPPS motif could be successfully utilized in the peptide of Example 2 of Alsina-Fernandez as well. EX1084 at ¶ 146. And in doing so, a POSA would reasonably expect that the exenatide tail would not only enhance the GLP-1 receptor binding activity of the peptide, but would also help to minimize immunogenicity. *Id*. Applying the exenatide tail to the Example 2 peptide of Alsina-Fernandez yields the following:


*Id*.

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

While Alsina-Fernandez and DiMarchi provide guidance for developing a co-GIP/GLP-1 agonist and provide rational design strategies for (1) enhancing binding affinity/potency for GIP and GLP-1 receptors, while (2) providing lower binding

affinity at the glucagon receptor, providing the desired selectivity, neither publication addresses the dosing frequency. EX1084 at ¶147.

A POSA was well-aware that the GIP/GLP-1 agonist peptides described in Alsina-Fernandez and DiMarchi (as well as the peptide sequence formed from the combination of the teachings of the two references) would need to be administered via injection. EX1084 at ¶148. Both Alsina-Fernandez and DiMarchi reference injecting the peptide formulations and it was well-known in the art that other GLP-1 agonist compounds were administered as injections. *Id.*; EX1007 at 25:4-6 ("Most preferably, such compounds are for parenteral administration"); EX1017 at 90:27-29 ("The compounds of the present invention can be used in some embodiments to prepare pre-formulated solutions ready for injection."); *see also* EX1054 (twice daily exenatide injection); EX1013 (once daily liraglutide injection); EX1050 (once daily liraglutide injection). It was also known that these compounds had a short half-life, meaning the compound would require regular administration to maintain therapeutic drug levels in the body—likely requiring daily injections. EX1084 at ¶148; *see, e.g.*, EX1054 at 3 (reporting a half-life of 2.4 hours); EX1013 at 14-15 (reporting that liraglutide has a half-life of 13 hours, suitable for once-daily administration); EX1050 at 12 (reporting that liraglutide has a 13-hour half-life).

Additionally, it was also well-known that many patients have "needle-phobia" and prefer medications with as few injections as possible – if injections are required,

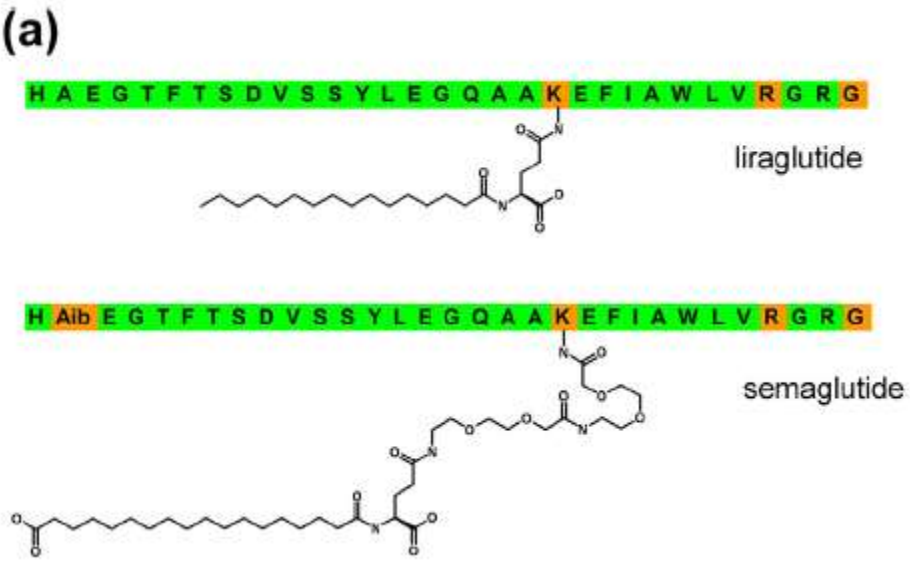
it would be preferred to have injections every several days, or once every week would be highly preferred. EX1084 at ¶149; EX1009 at 1:26-33.

While half-life values are not reported for the peptides in Alsina-Fernandez, a POSA would not expect that these peptides would support prolonged dosing (e.g., once-weekly dosing, or even dosing less than once per day). EX1084 ¶150. Example 2 of Alsina-Fernandez does not include an albumin-binding moiety, which was known prior to 2015 to significantly prolong half-life (as discussed, related to semaglutide). *Id*. Additionally, even the PEGylated peptides of Alsina-Fernandez (which a POSA would know to have longer half-lives because of their PEGylation) were still administered every three days when they were assessed *in vivo*. *Id*.; EX1007 at 19:18-20. Further, while the incorporation of the C-terminal exendin tail would be expected to prolong the half-life of the Example 2 peptide of Alsina-Fernandez (similar to what was achieved with exenatide, providing a half-life of ~2.4 hours), this prolonging would be limited to improved stability against proteolysis, and would not be expected to approach anything close to that required to provide once-weekly (or even less frequent than once daily), as evidenced by the fact that Byetta® (exenatide) was still required to be administered once daily. EX1084 ¶150 A major contributing factor is that, without binding to larger proteins (e.g., serum albumin), small peptides (such as Example 2 in Alsina-Fernandez and exenatide) generally are readily filtered by kidneys from the bloodstream. *Id*. Consequently, in

addition to enhancing the GIP/GLP-1 receptor potency (while minimizing glucagon receptor binding affinity), and also minimizing the potential for immunogenicity, a POSA was further motivated to address how to extend the half-life of the co-GIP/GLP-1 agonist formed from the combination of Alsina-Fernandez and DiMarchi to allow for extended dosing frequency (e.g., once weekly dosing). *Id*.

By 2013, researchers had begun to explore peptide design strategies to prolong the half-life and dosing frequency of GLP-1 compounds. EX1084 at ¶151. Lorenz discusses this approach with respect to GLP-1 analogs semaglutide and liraglutide, explaining that semaglutide is a "next-generation GLP-1 analog" with a ~160-hour half-life (allowing for once weekly administration). EX1084 at ¶¶151-152; EX1076 at 4014. Lorenz states that semaglutide demonstrated efficacy in both the treatment of Type 2 Diabetes Mellitus (as evidenced by reduction in HbA1c) and in providing weight-loss (4.8 kg weight reduction), even when administered once weekly. *Id*.

Specifically, Lorenz provides Fig. 2a, illustrating the fatty acid side chain modification utilized by liraglutide and semaglutide:




EX1084 at ¶153; EX1076 at 4014, Fig. 2a.

As illustrated in Fig. 2(a) above, Lorenz explains that, while there are multiple approaches for extending the half-life of GLP-1 agonists, "[l]iraglutide and semaglutide carry fatty acids, which facilitate binding to serum albumin thereby reducing their renal clearance." EX1076 at 4014, Fig. 2; EX1084 at ¶154. Therefore, in view of Lorenz, a POSA would have looked to guidance and teachings related to the semaglutide compounds and known structural modification strategies, including the use of fatty acid side chains to extend the half-life of GLP-1 and GIP co-agonist compounds (allowing for prolonged periods between doses). EX1084 at ¶155.

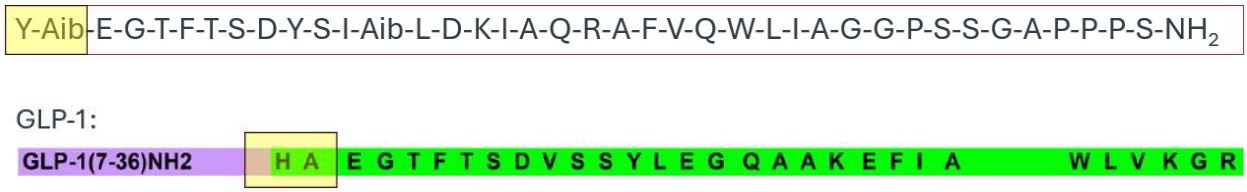
In doing so, a POSA would have identified Lau as Novo Nordisk's original patent on the semaglutide compound, with guidance on structural strategies for extending half-life. EX1084 at ¶156. Similar to the illustration in Fig. 2a of Lorenz, Lau discloses specific peptide design choices to prolong half-life and extend dosing

frequency, stating "there is a need to develop new GLP-1 compounds which can be administered less than once daily, e.g., once every second or third day[,] preferably once weekly, while retaining an acceptable clinical profile." EX1084 at ¶157; EX1009 at 1:31-34. Lau also explains that the decreased dosing frequency is achieved by conjugating the lysine residue in position 20 (pro-peptide position 26) of GLP-1 to an albumin-binding moiety that increases the duration of action of the GLP-1 analogue, stating that the GLP-1 analogs of the invention (1) have a modification of at least one non-proteogenic amino acid residue in positions 7 and/or 8 relative to the sequence GLP-1(7-37); and (2) are acylated with a moiety to the lysine residue in position 26 (corresponding to position 20 of the GLP-1 agonist compound). EX1084 at ¶157; EX1009 at 2:1-5. Lau teaches that this approach to prolonging the action of the agonist is applicable not only to the preferred GLP-1 analogues depicted therein, but also to other peptides with additional modifications to the amino acid sequence but which remain insulinotropic agents. EX1084 at ¶158; EX1009 at 3:8-4:8. Lau also teaches this approach to prolonged duration of action is useful because the acylated GLP-1 analogues can bind to albumin and the GLP-1 receptor simultaneously, such that they retain adequate affinity for the receptor. *Id*.; EX1009 at 6:6-22.

Regarding the design strategy related to modifying at least one non-proteinogenic amino acid at positions 7 and/or 8 relative to the GLP-1 sequence

(positions 1-2 of the GLP-1 agonist compound), Lau provides preferred substitutions at the 7 and/or 8 position, preferably Aib (α-aminoisobutyric acid) at position 8 (corresponding to position 2 of the GLP-1 agonist compound). EX1084 at ¶¶159-160; EX1009 at 8:12-15; 9:1-10; 11:11-12; 17:13; 17:32; 18:29-30; 19:1-2; 19:25-26; 19:30-31. In fact, the semaglutide compound described in both Lorenz and Lau includes Aib at position 8 (position 2 of the GLP-1 agonist compound). *Id*.; EX1076 at 4014, Fig. 2a; EX1009 at 47:4-22, Example 4. Based on this disclosure, a POSA was motivated to utilize Aib as a non-proteogenic amino acid residue at position 8 (position 2 of the GLP-1 agonist compound), as Lau teaches that Aib is a preferred residue at that position and the semaglutide compound similarly incorporated Aib at position 2. EX1084 at ¶160.

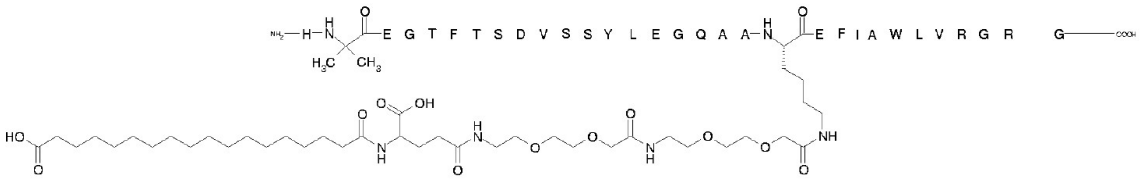
Below is an illustration of the peptide sequence rendered obvious by Alsina-Fernandez (lead compound/reference) and DiMarchi, discussed previously:




EX1084 at ¶161. As highlighted in yellow by Dr. Zhou, the peptide compound based on the teachings of Alsina-Fernandez in view of DiMarchi already incorporates modifications at positions 7 and 8 (positions 1 and 2 of the peptide compound), including the preferred Aib residue at position 2, meaning this design strategy was

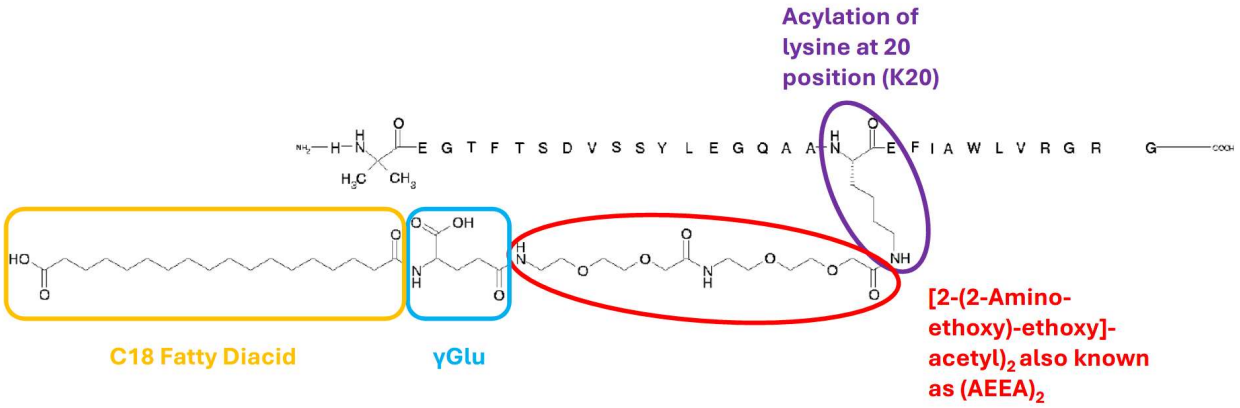
already incorporated into the compound formed by Alsina-Fernandez in view of DiMarchi. EX1084 at ¶162.

Because this design strategy was already accounted for, a POSA would have then turned to the second design strategy described by Lau to further prolong the duration of effect, namely acylation of the lysine residue at GLP-1 position 26 (corresponding to position 20 of the GLP-1 agonist compound). EX1084 at ¶163. For reference, Example 4 of Lau illustrates the chemical structure for semaglutide, as shown below:



EX1084 at ¶163; EX1009 at 47:4-22.

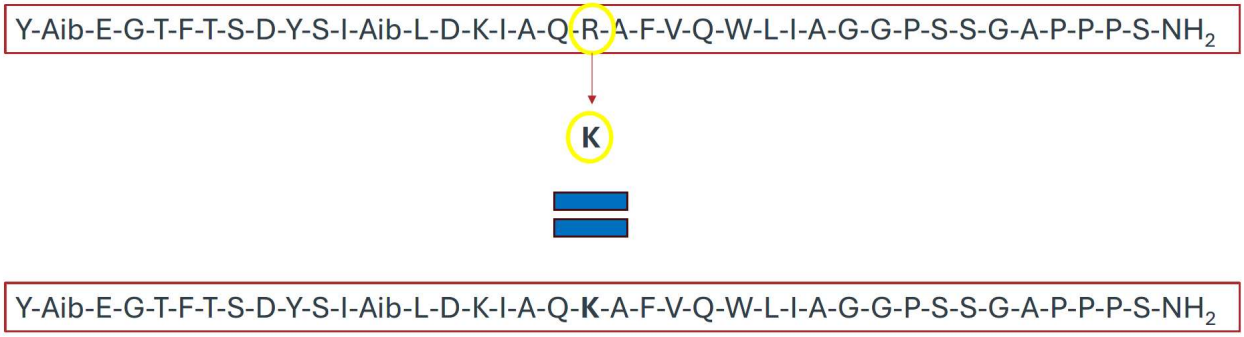
To further illustrate, Dr. Zhou has provided an annotated copy of the semaglutide structure, noting the acylation of the lysine at position 20 of the semaglutide molecule, as well as the specific components of the acylation moiety:



EX1084 at ¶164. As shown above, the semaglutide structure is acylated at the lysine in position 20 (noted in purple), whereby the spacer is conjugated to the amine side chain of the lysine. EX1084 at ¶165. Additionally, the spacer of semaglutide consists of both the 2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$ (noted in red) and the gamma-glutamate (noted in blue). *Id*. Finally, semaglutide incorporates a C18 fatty diacid (noted in gold). *Id*.

Turning first to semaglutide's incorporation of a lysine at the 20 position of the sequence, DiMarchi teaches that the Arg (R) present at position 20 in the Alsina-Fernandez/DiMarchi peptide can be replaced with a lysine (K), stating "[i]n some embodiments the amino acid at position 20 is substituted with Ser, Thr, **Lys**, Arg, Orn, Citrulline or AIB." EX1084 at ¶166; EX1017 at 40:7-8. Additionally, the native GLP-1 peptide has a lysine (Lys) residue at position 26 (i.e., position 20 of the GLP-1 agonist compound). EX1084 at ¶166. As discussed previously, where possible, preserving native amino acid sequence is generally preferred, as it can help to minimize immunogenicity, so in this instance a POSA would have been further motivated to utilize Lys at position 26 (i.e., position 20 of the GLP-1 agonist compound) from among the options disclosed by DiMarchi. *Id*. Further, because Lau expressly focuses its design strategy on acylation of a lysine (K) at position 26 relative to GLP-1 (i.e., position 20 of the GLP-1 agonist compound), a POSA was motivated to replace the arginine (R) in the Alsina-Fernandez/DiMarchi peptide with

lysine (K), as that was permitted by the teachings of DiMarchi, and the semaglutide compound successfully incorporated this change, as shown in the illustration below:



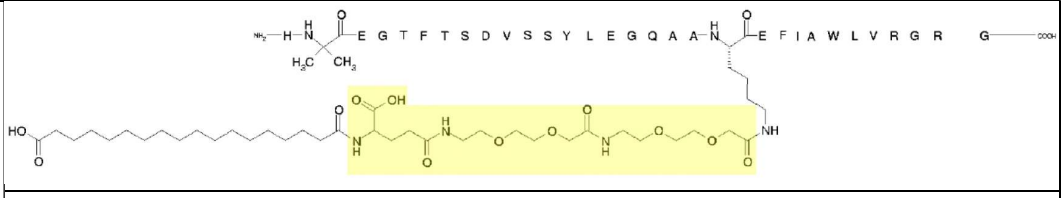
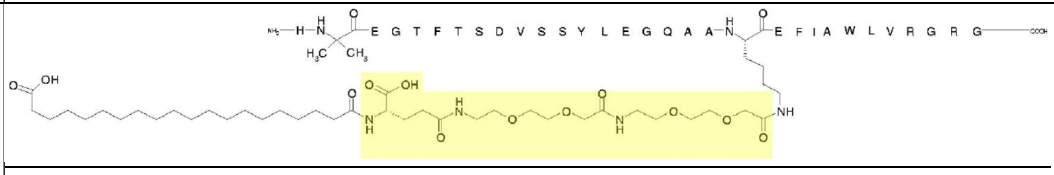
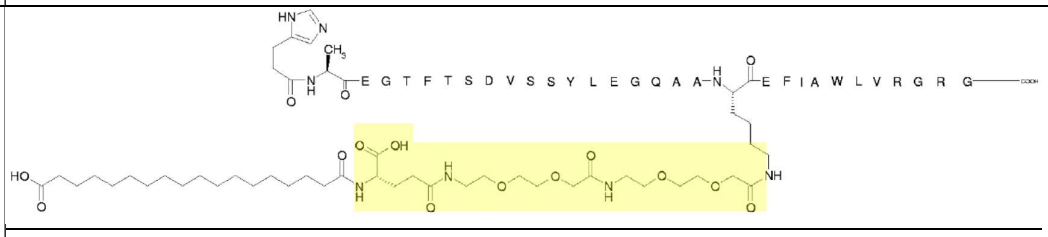
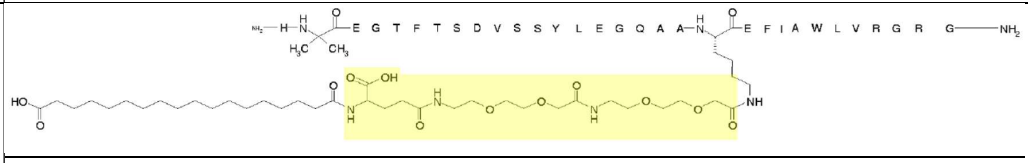
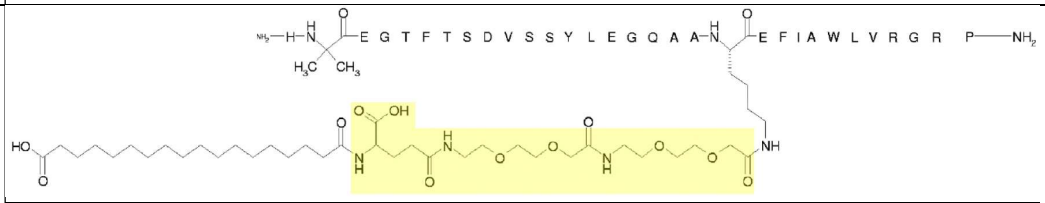
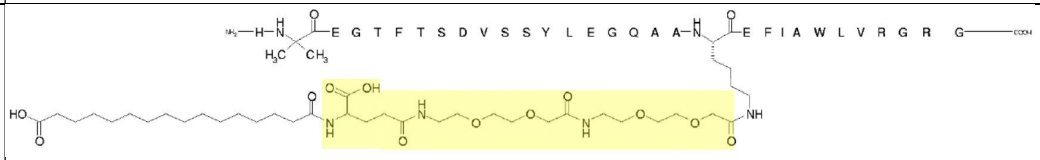
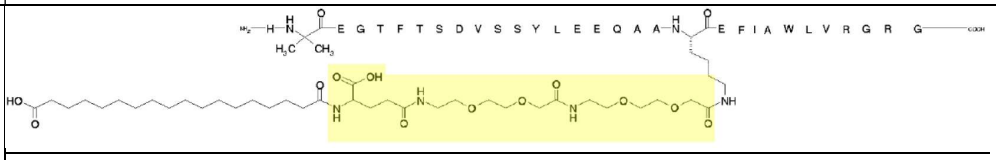

*Id*.

Additionally, DiMarchi discusses that acylation can be achieved via a spacer (e.g., an amino acid, dipeptide, tripeptide, hydrophilic bifunctional spacer, hydrophobic bifunctional spacer), and that acylation can improve half-life and resistance to deactivation. EX1084 at ¶167; EX1017 at 7:7-10, 56:3-8. DiMarchi also states that "[a]cylation can be carried out at any position within the glucagon peptide, including any of positions 1-29." EX1017 at 56:29-57:1; 58:8-17. However, DiMarchi identifies preferred amino acids and locations for acylation, including the amino acid at position 20 (which, as noted above, was preferably a lysine (K)). EX1084 at ¶167; EX1017 at 58:8-17. This was consistent with not only the teachings in Lau related to semaglutide (directed to acylation specifically at the $Lys^{20}$ position), but also Madsen et al., which assessed the impact of acylating peptides with fatty acids of vary lengths on half-life, all of which were acylated at the lysine at position 26 of native GLP-1 (corresponding to position 20 of the GLP-1 agonist compound).

EX1079, 6126-6127. Given all these factors, a POSA would have been motivated to acylate the lysine at position 20 of the Alsina-Fernandez/DiMarchi peptide, and would reasonably expect that the lysine at position 20 could be successfully acylated.

DiMarchi also teaches that the spacer can be attached to the amine side chain of lysine (K), stating that "[i]n the instance in which the side chain amine of the spacer amino acid is acylated, the spacer amino acid is an amino acid comprising a side chain amine, e.g., an amino acid of Formula I (e.g., **Lys** or Orn)." EX1084 at ¶168; EX1017 at 60:19-23. Consequently, DiMarchi expressly contemplated the attachment of a spacer to the lysine at position 20, similar to the design strategy utilized for semaglutide (as described in Lau). EX1084 at ¶168.

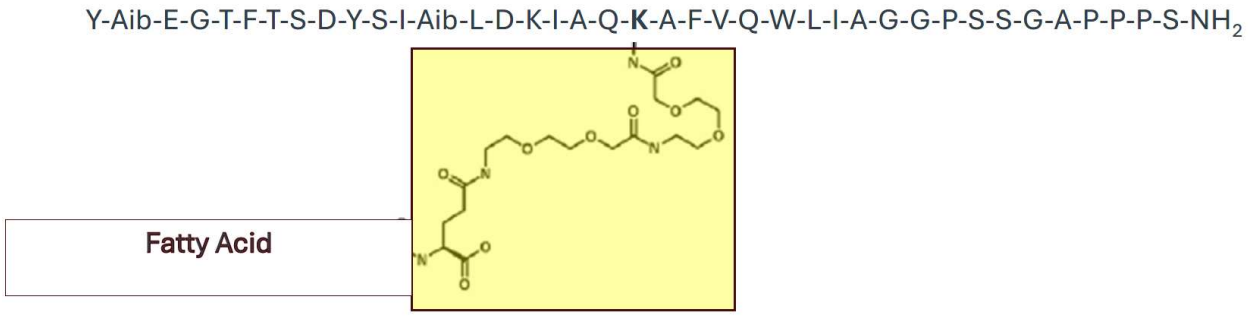
Regarding specific compounds to be utilized as the spacer, Lau explains that the spacer is a "hydrophilic linker" that separates the peptide and the albumin binding residue. EX1084 at ¶169; EX1009 at 6:22-24. In addition, many of the Examples of Lau (including, e.g., Examples 4, 5, 6, 10, 11, and 15) utilize a specific spacer compound, namely a [2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer. *Id*. To illustrate, Dr. Zhou provides tables below with the structure of each of the peptides of Examples 4, 5, 6, 10, 11, and 15, with the spacer moiety highlighted in yellow:

| Example | Structure with Spacer Highlighted |
|---|---|
| 4 |  |
| 5 |  |
| 6 |  |
| 10 |  |
| 11 |  |
| 12 |  |
| 15 |  |

EX1084 at ¶169; EX1009 at 47:4-9 (Example 4), 47:22-28 (Example 5), 48:12-18 (Example 6), 50:6-11 (Example 10), 50:22-28 (Example 11), 51:6-10 (Example 12), 52:12-16 (Example 15).

As illustrated in the table above, Lau teaches the inclusion of the same [2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer (also known as an AEEA-AEEA-γGlu spacer) to attach the fatty acid (of various lengths) to the lysine at the 20 position of the peptide (in the structures of Examples 4, 5, 6, 10, 11, 12, and 15, the lysine is represented by its full chemical structure to illustrate the binding position, rather than the shorthand "K"). EX1084 at ¶170. Indeed, Example 4 above is the semaglutide compound, which is shown utilizing the same [2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer, and using this spacer to attach a C18 fatty diacid to the peptide sequence. *Id*. In view of the teachings of Lau and DiMarchi, and in view of Lau's teachings that the semaglutide compound was shown to have an ~160 hour half-life (allowing for once weekly administration), a POSA would have been motivated to utilize the same [2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer, attached to the lysine at the 20 position of the peptide based on the teachings of Alsina-Fernandez in view of DiMarchi and Lau. *Id*. Additionally, a POSA would reasonably expect that this same spacer can be utilized in the Alsina-Fernandez/DiMarchi peptide, as it was shown to be successfully incorporated into semaglutide, and successfully extended the duration of action. Dr. Zhou illustrates

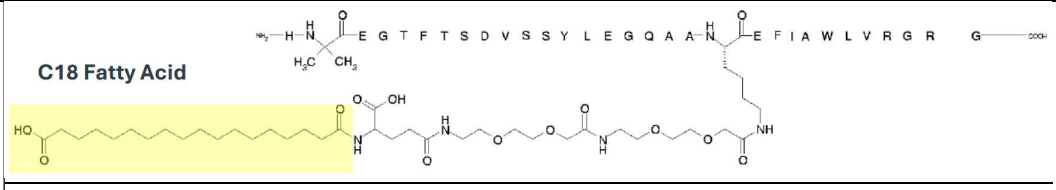
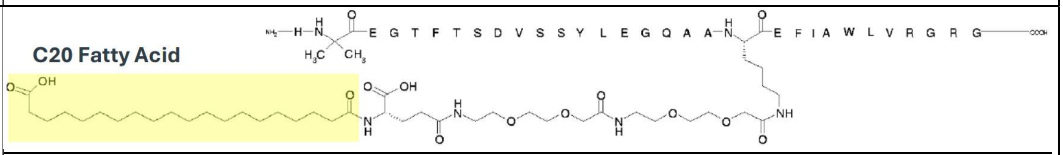
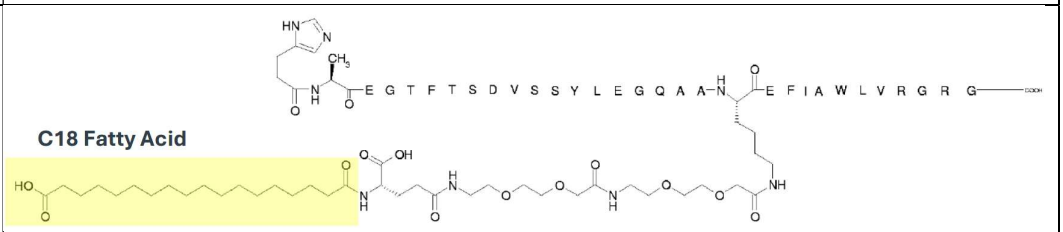
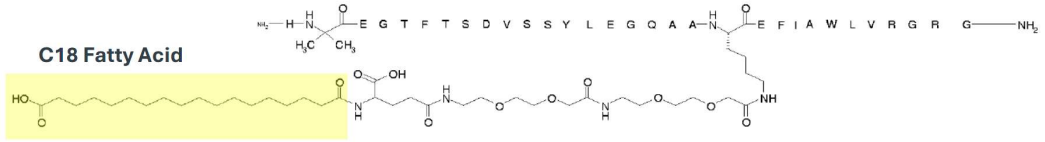
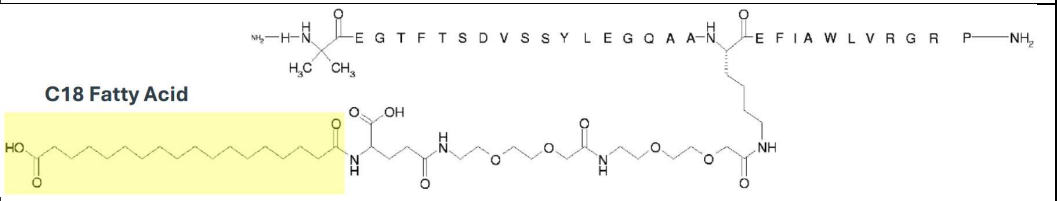
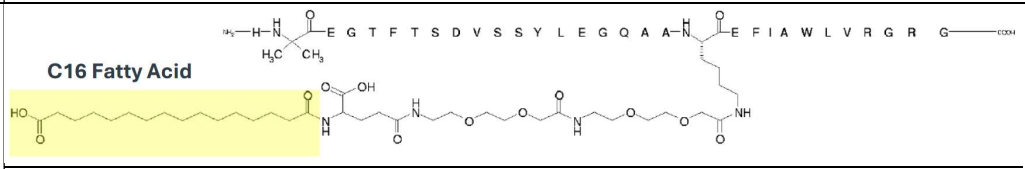
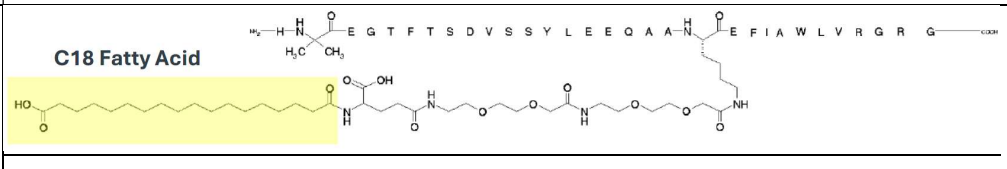
this structural modification below (the [2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu) spacer highlighted in yellow):




*Id*.

Moreover, DiMarchi teaches that the acyl group (used for the aforementioned acylation) may be a fatty acid, stating that "[i]n some embodiments, the acyl group is a fatty acid or bile acid, or salt there, e.g., a C4 to C30 fatty acid, a C8 to C24 fatty acid, cholic acid, a C4 to C30 alkyl, a C8 to C24 alkyl, or an alkyl comprising a steroid moiety of a bile acid." EX1084 at ¶171; EX1017 at 56:17-19. In fact, DiMarchi specifically identifies C4 to C30 fatty acids as potential options, and focuses on *C8 to C20 fatty acids* as preferred options. *Id*.

DiMarchi's teachings are entirely consistent with the teachings of Lau. EX1084 at ¶172. Although Lau does not discuss specific fatty acids attached to the peptides via the spacer, the structures provided in the Examples of Lau illustrate that C16, C18 and C20 fatty acids (diacids) were preferably utilized. Dr. Zhou provides the table below to illustrate the fatty acids utilized in Lau's examples:

| Example | Structure with Fatty Acid Highlighted |
|---|---|
| 4 |   |
| 5 |   |
| 6 |   |
| 10 |   |
| 11 |   |
| 12 |   |
| 15 |   |