Filed on behalf of: Eli Lilly & Co.

Entered: September 22, 2025

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
Patent 9,474,780

PATENT OWNER'S PRELIMINARY RESPONSE

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2087	Eli Lilly & Co., Presentation: Q2 2025 Earnings Call (Aug. 7, 2025), https://investor.lilly.com/static-files/b7c7e82b-e667-42ba-827c-1faecba3e4c8

I. INTRODUCTION

Patent Owner Eli Lilly & Co. ("Lilly" or "Patent Owner") respectfully requests that the Board deny institution of the Petition for *inter partes* review filed by Empower Clinic Services, LLC (d/b/a Empower Pharmacy) ("Petitioner") challenging U.S. Patent No. 9,474,780 (the "'780 patent"). The '780 patent protects tirzepatide, the active ingredient of Lilly's revolutionary drug products for the treatment of diabetes, obesity, and sleep apnea, Mounjaro® and Zepbound®. Since their launches, Lilly's tirzepatide products have collectively generated over $37 billion worldwide in revenue and are projected to earn over $31 billion in sales in 2025 alone. On top of its marketplace success, tirzepatide has garnered widespread praise in the medical industry, including the prestigious Prix Galien Award in biopharmaceutical research. Tirzepatide's success and acclaim flow from Lilly's significant research and development investments in a highly unpredictable art, where multiple companies tried but failed to achieve similar results. Rather than investing in its own R&D, Petitioner copied Lilly's invention, touting tirzepatide as a "novel" GIP/GLP-1 dual agonist "advancing beyond traditional GLP-1 therapy."

Yet now, Petitioner asks this Board to find that tirzepatide was obvious all along. Its sole Ground relies on three references—Alsina-Fernandez, Just, and Lau—all of which were considered by or are cumulative of references considered during prosecution. Because none disclose the claimed compounds, Petitioner

argues that it would have been obvious to pick components of each and stitch them together to arrive at the claimed invention. Petitioner's argument suffers from four fundamental flaws, each of which is reason enough to deny institution.

First, the Petition uses hindsight to select its lead compound without even attempting to show—as legally required—how a skilled artisan would have chosen it over any of a multitude of other prior art candidates, including the only GIP/GLP-1 dual agonist with a publicly known structure that had progressed to human trials. Institution should be denied on this basis alone.

Second, Petitioner applies hindsight on top of hindsight to pick and choose a litany of specific modifications—and no others—from countless options in the prior art to arrive at the claimed invention. Petitioner attempts to characterize its path from lead compound to claimed invention as involving "three" straightforward changes purportedly motivated by "good reasons," but its analysis fails on multiple levels. For starters, Petitioner fails to show that a skilled artisan would have made ***any*** changes at the relevant locations, much less the specific changes it proposes. In addition, Petitioner's characterization of needing to make only three changes badly misses the mark; at best there are three ***categories*** of changes, each implicating multiple decision points with many options at each, culminating in ***countless*** possibilities. Petitioner's only roadmap is the challenged patent itself—which, of course, the skilled artisan would not have had.

Third, Petitioner fails to establish a reasonable expectation of success. Despite Petitioner's arguments otherwise, developing effective dual agonists was a highly unpredictable art, with skilled artisans viewing dual agonist "drug discovery [as] challenging, and perceived by some to be ***almost impossible***," because dual agonists "need to be optimized against multiple biological targets, [which] poses additional hurdles." Creating a new dual agonist by making multiple changes to a lead compound—as Petitioner's obviousness theory requires—risks unexpected consequences and dramatically increases unpredictability.

Fourth, the Petition ignores objective indicia that strongly and unanimously confirm non-obviousness. While Petitioner feigns ignorance of any objective indicia (Pet. 78-80), it promotes its tirzepatide knock-offs by emphasizing many of these same facts. *Failure of others and long-felt unmet need*: At the time of Lilly's invention, other companies and research teams were trying to develop GIP/GLP-1 dual agonists, but all failed. To date, tirzepatide is the *only one* to have received FDA approval, satisfying a longstanding need for an improved obesity, diabetes, and sleep apnea treatment. *Industry praise*: Tirzepatide received the Prix Galien, the highest honor in the pharmaceutical industry. *Commercial success*: Tirzepatide is one of the most successful drugs in history, with over $31 billion in projected sales this year alone. *Unexpected results*: Tirzepatide demonstrates superior efficacy and tolerability to prior art compounds. *Copying*: Petitioner copied tirzepatide and touts

tirzepatide's novelty and improvement over prior therapies—just the opposite of what it is telling the Board today.

Because Petitioner fails to demonstrate a reasonable likelihood of unpatentability, the Board should deny institution.

II. OVERVIEW OF THE '780 PATENT AND THE PRIOR ART

A. The '780 Patent (Ex. 1001)

The '780 patent, entitled "GIP and GLP-1 Co-Agonist Compounds," discloses "dual incretin peptide mimetic compounds that agonize receptors for both human glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1)." '780 Patent, Title, Abstract.

GIP plays a role in balancing glucose levels in the human body by stimulating insulin secretion from pancreatic beta cells in the presence of glucose. *Id.*, 1:21-24. GLP-1 stimulates insulin secretion, protects pancreatic beta cells, and inhibits glucagon secretion, gastric emptying and food intake. *Id.*, 1:25-28. GIP and GLP-1 (known as incretins), are secreted from the gut following a meal; these incretins enhance the physiological response to food, including sensation of satiety, insulin secretion, and nutrient disposal. *Id.*, 1:30-34. Individuals with type 2 diabetes have impaired incretin responses. *Id.*, 1:34-35.

Prior art GLP-1 monoagonists were limited by adverse effects, including nausea and vomiting, which hindered them from reaching full efficacy for glycemic

control and weight loss. *Id.*, 1:36-39. GIP alone has very modest glucose-lowering ability in people with type 2 diabetes, and both GIP and GLP-1 degrade rapidly, and therefore can only be used for short-term metabolic control. *Id.*, 1:39-43. Furthermore, these types of molecules can cause immunogenicity issues and injection site reactions. *Id.*, 1:66-2:3. In addition, closely related receptors for glucagon and GLP-2 were tied to blood glucose elevation and carcinogenic risk, respectively, raising concerns about off-target effects. *Id.*, 1:45-54.

The '780 patent cites several prior art references that described GIP/GLP-1 dual agonists. *Id*., 1:55-57. But these references lack any teaching to show they would overcome the limitations of prior art monoagonists. *See generally* Ex. 1008 (WO 2013/164483, "Just"), Ex. 2001 (WO 2014/192284, "Asami"), and Ex. 1007 (WO 2011/119657, "Alsina-Fernandez").

To this day, tirzepatide is the only GIP/GLP-1 dual agonist that has received FDA approval. Ex. 2002 (Lilly Press Release (May 13, 2022)). But this is not for lack of effort: the prior art is littered with examples of failed attempts. For instance, Just embodies Zealand Pharma's extensive—and failed—efforts to develop GIP/GLP-1 dual agonists at the same time as Lilly. Despite identifying billions of possible GIP/GLP-1 dual agonists more than 12 years ago in 2013, Zealand Pharma has failed to develop a single FDA-approved GIP/GLP-1 dual agonist. *See infra* Section II.C. Similarly, Marcadia (subsequently acquired by Roche, and later Novo

Nordisk), spent years trying to develop GIP/GLP-1 dual agonists, but ultimately abandoned their efforts. Ex. 2066 (Lorenz 2013), 4016 (reporting that "MAR701 (RO-6807952) … was discontinued in September 2012 and replaced by a follow-up compound MAR709 (RG7697/RO6811135)"); Ex. 2053 (Müller 2022), 212 (reporting discontinuation of "NN9709 (formerly MAR709 and RG7697)"). Likewise, Asami embodies Takeda's contemporaneous, but unsuccessful, efforts to develop a GIP/GLP-1 dual agonist.

Based on these limitations in the prior art and the substantial unpredictability in the field, before the '780 patent, "[t]here remain[ed] a need to provide a compound that is a balanced co-agonist of GIP and GLP-1 receptors, but is selective against related glucagon and GLP-2 receptors." '780 Patent, 2:27-29. There was also a need for a balanced GIP/GLP-1 co-agonist that provided "improve[d] glycemic control in adults with type 2 diabetes mellitus" and adequate stability against dipeptidyl peptidase-4 and other routes of degradation, while still maintaining a low immunogenicity potential. *Id.*, 2:33-37, 5:45-49. Prior to the '780 patent, "[t]olerability of certain GLP-1 analogues has been found to prevent a dose of the GLP-1 analogue that reaches better efficacy for glycemic control and weight loss." *Id.*, 2:12-14. In addition, there was a need for a GIP/GLP-1 co-agonist that supported once-weekly dosing. *Id.*, 2:37-40.

The '780 patent discloses and claims compounds that meet these needs. As the '780 patent explains:

> Accordingly, certain compounds of the present invention have lower potential for immunogenicity and injection site reactions than certain GIP-GLP-1 co-agonist compounds in the art. Certain compounds of the present invention have potential for producing weight loss in patients …. Furthermore, certain compounds of the present invention have a balanced co-agonist activity against GIP and GLP-1 receptors and selectivity against both glucagon and GLP-2 receptors, low immunogenicity potential, and pharmacokinetic (PK) characteristics that support once-weekly dosing in humans.

Id., 2:41-52.

Independent claim 1 of the '780 patent recites:

> 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)$_2$-(γGlu)$_a$-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;

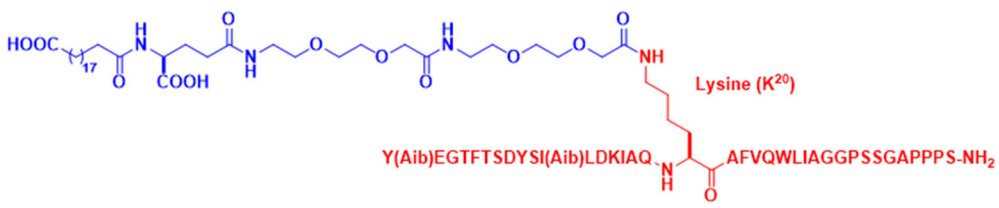
> and the C-terminal amino acid is optionally amidated as a C-terminal primary amide (SEQ ID NO: 11),
>
> or a pharmaceutically acceptable salt thereof.

Id., cl. 1. The claim recites a genus of compounds that includes tirzepatide, the active pharmaceutical ingredient in Lilly's groundbreaking Mounjaro® and Zepbound® products indicated for the treatment of type 2 diabetes (Mounjaro®), and obesity and sleep apnea (Zepbound®). *Id.*

As Lilly explained in a subsequent patent application, tirzepatide is a "GIP/GLP1 co-agonist peptide as described … in Example 1 of [the '780 patent]." Ex. 2054 (USP 11,357,820), 3:19-33. Tirzepatide has the following sequence:

> $YX_1EGTFTSDYSIX_2LDKIAQKAFVQWLIAGGPSSGAPPPS$
> 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-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-(γGlu)$_1$-CO—$(CH_2)_{18}$—CO_2H; and the C-terminal amino acid is amidated as a C-terminal primary amide (SEQ ID NO: 3).

'780 patent, 8:56-67. Tirzepatide thus meets every limitation of claim 1 of the '780 patent. Tirzepatide is also recited in claim 15 of the '780 patent, which depends from claim 1, and has the following structure:



See id., cl. 15 (structure abbreviated and annotated).

Tirzepatide is a synthetically produced alpha amino acid polymer that contains 42 amino acids, comprising (1) a backbone of 39 amino acids (shown in red in the image above), as well as (2) a second (associated or "side") chain of one residue of gamma-glutamate and two residues of 8-amino-3,6-dioxaoctanoic acid (which together form a "linker" or "spacer") and a fatty acid (which collectively are shown in blue in the image above). This brief refers to the amino acid "backbone" to discuss the 39 amino acids shown in red above and refers to the "compound" when discussing the entire molecule, including both the red and blue portions.

B. WO 2011/119657 A1 (Alsina-Fernandez) (Ex. 1007)

Alsina-Fernandez describes Lilly's early efforts to develop GIP/GLP-1 dual agonist compounds. It discloses and claims "GIP analogs with amino acid substitutions introduced to modulate activity for both GIP-R and GLP-1-R and maintain selectivity over Gluc-R." Alsina-Fernandez, 1:6-7.

Petitioner relies on Alsina-Fernandez specifically for its disclosure of a genus of GIP/GLP-1 dual agonists defined by SEQ ID NO:1:

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.

Id., 2:12-25. Petitioner identifies SEQ ID NO:1 as the "lead compound" in its obviousness theory (Pet. 26, 76-77), even though Alsina-Fernandez itself identifies Example 5 (SEQ ID NO:3) as the "most preferred embodiment of the present invention." Alsina-Fernandez, 3:25-31.

Alsina-Fernandez discloses five working examples of compounds within the genus defined by SEQ ID NO:1, along with results of their *in vitro* and *in vivo* (mouse and rat) testing. *Id.*, 8-11. Examples 1 and 2 are not PEGylated, while Examples 3-5 are PEGylated. *Id.*

Compound	Amino Acid Sequence & Functional Groups
'780 Patent (SEQ ID NO:3)	(AEEA-AEEA-γGlu-C20 diacid) | YXEGTFTSDY SIXLDKIAQK AFVQWLIAGG PSSGAPPPS
Alsina-Fernandez (Example 1; SEQ ID NO:4)	YXEGTFTSDY SIXLDKIAQR AXVQWLIAXK GKKQEWKHQI TQ
Alsina-Fernandez (Example 2; SEQ ID NO:5)	YXEGTFTSDY SIXLDKIAQR AFVQWLIAXK GKKQEWKHQI TQ
Alsina-Fernandez (Example 3; SEQ ID NO:2)	YXEGTFTSDY SIXLDKIAQR AFVQWLIAXK GKKQEWKHQI TQC(PEG20K)C(PEG20K)
Alsina-Fernandez (Examples 4/5; SEQ ID NO:3)	YXEGTFTSDY SIXLDKIAQR AXVQWLIAXK GKKQEWKHQI TQC(PEG20K)C(PEG20K)

C. WO 2013/164483 A1 (Just) (Ex. 1008)

Just is a published patent application by Zealand Pharma, entitled "GIP-GLP-1 Dual Agonist Compounds and Methods." Just states, "[b]roadly, the present invention concerns truncated GIP analogues which comprise one or more substitutions as compared to wild-type GIP and which may have the property of an altered, preferably increased GLP-1 activity, e.g., as assessed in *in vitro* efficacy assays." Just, 2:24-27.

Petitioner relies on Just for the disclosure of multiple limitations of the challenged claims, including an exenatide C-terminal motif[1] and acylation. When accounting for all of the various optional amino acid substitutions in the 14 genus formulas of Just's "GIP analogues of the invention" (*id.*, 3:7-16:19), and the myriad different lipophilic substituents and spacer molecules that may be conjugated at "one or more of" eight different amino acid positions (*id.*, 49:2-52:17), Just's generic formulas disclose innumerable compounds—at least billions.

Just discloses 56 working examples of GIP/GLP-1 dual agonists, but: (1) the vast majority do not contain an exenatide C-terminal motif; (2) none have a glycine

[1] Petitioner's "exenatide C-terminal motif" is derived from the C-terminal amino acid sequence of exendin-4, an ortholog of GLP-1 found in the Gila monster. Exenatide is a synthetic analog of exendin-4.

at position 29 as required by the challenged claims; and (3) most are not acylated, and those that are have the fatty acid chain attached at position 17, not at position 20 as required by the claims. Just, 65-67 (Tables 1-2).

Just discloses *in vitro* test results for 53 of the 56 working examples. *Id.*, 69:1-71:2 (Example 2). But Just discloses *in vivo* (mouse) results for only two compounds, nos. 32 and 33, both of which differ from the claimed compounds in the position of fatty acid attachment, choice of albumin-binding moiety, and multiple amino acids in the amino acid backbone. *Id.*, 71:6-72:35 (Examples 3-5, Figs. 1-7).

D. WO 2006/097537 A2 (Lau) (Ex. 1009)

Lau is a published patent application by Novo Nordisk, entitled "Acylated GLP-1 Compounds." In contrast to Alsina-Fernandez and Just, which disclose GIP/GLP-1 dual agonists, Lau discloses only GLP-1 monoagonists.

Petitioner relies on Lau for its disclosure of a specific albumin binding moiety conjugated to some of its GLP-1 agonists. But, when considering all of the various options for different fatty acid side chains and hydrophobic linkers, Lau discloses at least thousands of acylated moieties. Lau, 7:29-17:10 (disclosing acylated moieties defined by B-U', with an exceedingly high number of variables).

Lau does not include any *in vitro* or *in vivo* data for any of the disclosed compounds, and therefore Lau does not contain any information from which a skilled artisan could determine a structure-activity relationship ("SAR") for the

compounds. Accordingly, a skilled artisan would have no way of determining from Lau which acylated moieties are better than any of the others.

III. PROSECUTION HISTORY

The Examiner allowed the claims of the '780 patent without any prior art rejections. *See generally* Ex. 1004 ("'780 Patent FH"). She did so after reviewing and considering the same or cumulative prior art as asserted by Petitioner.

Just was (1) cited in the specification of the application that issued as the '780 patent (*id.*, 89; '780 Patent, 1:55-57), (2) identified in an information disclosure statement ("IDS") ('780 Patent FH, 36-40), and (3) distinguished in the Examiner's Reasons for Allowance as the closest prior art (*id.*, 27-28). The Examiner explicitly stated that Just was "[t]he closest prior art" and still found the '780 patent claims allowable. *Id.*

Alsina-Fernandez was cited twice in the specification of the application that issued as the '780 patent. *Id.*, 89, 114; '780 Patent, 1:55-57, 20:54-64. The Examiner reviewed the specification of the application leading to the '780 patent and the art cited therein, including Alsina-Fernandez, and determined that the claims were patentable over Alsina-Fernandez.

Semaglutide, which underlies Petitioner's reliance on Lau, was referenced in the specification of the '780 patent ***28 times***. '780 Patent FH, 98 (identifying "semaglutide" by its structure); '780 Patent, 8:23-26 (same). The claimed

compounds were compared to semaglutide in *in vivo* assays of insulin secretion; body weight or fat mass change; blood glucose, plasma cholesterol, and plasma and liver triglyceride levels; gastric emptying; and plasma corticosterone levels. '780 Patent FH, 116-125; '780 Patent, Tables 7-9, 11-12, 14-15. Based on this testing, Lilly concluded that the claimed compounds exhibiting dual agonist activity have advantages over the monoagonist semaglutide. '780 Patent FH, 116-125; '780 Patent, 22:18-28:17. Again, the Examiner reviewed the specification of the application that issued as the '780 patent and the art cited therein, including the disclosure of semaglutide, before finding the claims patentable.

In allowing the claims, the Examiner considered and rejected the same reasoning underlying Petitioner's obviousness arguments, finding that making specific changes necessary to arrive at the claimed compounds—and no others—would have required hindsight. With respect to Just, the Examiner explained that to make the claimed compounds, a skilled artisan would have had "to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different from those preferred and reduced to practice in [Just]." '780 Patent FH, 28. Then, a skilled artisan would need "to substitute a Gln at position 24 and a moiety of ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)$_2$-($_\gamma$Glu)$_{1\text{-}2}$-CO-(CH$_2$)$_{10\text{-}20}$-CO$_2$H) for the lipophilic substituent, but not make any other changes." *Id.* "***To do so would require hindsight reasoning***." *Id.* The Examiner noted that there is "no teaching or

suggestion in [Just]" that would suggest the Gln24 and lipophilic substituent modifications and "[e]ven if there were," making those specific changes and no others would "require hindsight reasoning." *Id.*, 27-28.

IV. PETITIONER'S OBVIOUSNESS ARGUMENT FAILS

The Petition asserts that the challenged claims[2] would have been obvious but does not come close to establishing a reasonable likelihood of unpatentability. Its sole Ground fails for four independent reasons. The Petition fails to (1) show, or even assert, that its proposed lead compound was properly selected, (2) establish that there would have been a motivation to combine the prior art references as it proposes, (3) show that there would have been a reasonable expectation of success in doing so, or (4) address the substantial evidence of objective indicia confirming the non-obviousness of the claimed inventions. Petitioner's obviousness theory is guided by

[2] Solely for purposes of this Preliminary Response, Lilly focuses on claim 1 of the '780 patent because it is the broadest claim, and because it is nonobvious, the dependent claims are necessarily nonobvious as well. *See Skechers U.S.A., Inc. v. Nike, Inc.*, IPR2025-00144, 2025 WL 1691041, at *8 (P.T.A.B. June 16, 2025) ("Dependent claims are nonobvious under section 103 if the independent claims from which they depend are nonobvious." (quoting *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988))).

hindsight at every turn. "Any compound may look obvious once someone has made it and found it to be useful, but working backwards from that compound, with the benefit of hindsight, once one is aware of it does not render it obvious." *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019).

A. Petitioner's Lead Compound Selection Is Legally Deficient

The Board and the Federal Circuit have established a specific test to evaluate obviousness challenges to chemical compound patents like the '780 patent—the lead compound test. *See, e.g.*, *Mylan Pharms. Inc. v. Novo Nordisk A/S*, IPR2023-00722, Paper 9 at 13-14 (P.T.A.B. Oct. 2, 2023) (describing the Federal Circuit's "two-prong analysis to determine whether a new chemical compound is prima facie obvious over particular prior art"); *Sawai USA, Inc. v. Astellas Pharma Inc.*, IPR2018-00079, Paper 7 at 13 (P.T.A.B. May 4, 2018) ("[T]he lead compound analysis for new chemical compounds is a well-established practice in *inter partes* review." (citing cases)). The lead compound test is a two-part inquiry:

> First, the court determines whether a chemist of ordinary skill would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.… The second inquiry in the analysis is whether the prior art would have supplied one of ordinary skill in the art with a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success.

Otsuka Pharm. Co. v. Sandoz, Inc., 678 F.3d 1280, 1290-92 (Fed. Cir. 2012).[3]

Petitioner fails to satisfy even the first prong of the lead compound test, selecting its lead compound based entirely on hindsight and devoid of any showing that a skilled artisan "would have had a reason to select a proposed lead compound or compounds ***over other compounds in the prior art***." *Daiichi Sankyo Co. v. Matrix Laboratories, Ltd.*, 619 F.3d 1346, 1354 (Fed. Cir. 2010); *see also Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357, 1359-60 (Fed. Cir. 2007) (affirming deficiency of lead compound selection where "the prior art disclosed a broad selection of compounds" and there was "nothing in the prior art to narrow the possibilities"); *Otsuka*, 678 F.3d at 1292 ("[O]ur analysis focuses on those proposed lead compounds … that the skilled artisan would have had a reason to select from the panoply of known compounds in the prior art."). Lead compound selection must be "guided by evidence of the [proposed] compound's pertinent properties," which "may include positive attributes such as activity and potency, … adverse effects such as toxicity, … and other relevant characteristics in evidence." *Otsuka*, 678 F.3d at 1292. Critically, "[a]bsent a reason or motivation based on such

[3] Emphases added and internal quotation marks and citations omitted throughout unless otherwise indicated.

prior art evidence, mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection." *Id.*

Petitioner does not even ***attempt*** to make the required showing. In fact, Petitioner does not even assert that a skilled artisan would have selected its lead compound[4] "over other compounds in the prior art." *See Daiichi*, 619 F.3d at 1354. Indeed, the Petition does not mention ***any*** other potential lead compounds, much less discuss or compare them to its hindsight-informed selection. The Petition's only explanation of its lead compound selection is contained in two conclusory sentences, without any of the required analysis, as reproduced below:

> 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.
>
> * * *

[4] For simplicity, Lilly refers to Alsina-Fernandez's SEQ ID NO:1 as Petitioner's "lead compound," but Petitioner's lead compound is actually a genus encompassing 28 distinct compounds. *See* Alsina-Fernandez, 2:12-25.

> 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.

Pet. 26, 76-77. Petitioner's circular logic, that a skilled artisan would identify the lead because it would be improved if it was further modified, renders the process of selecting a lead compound meaningless. Many other compounds might be improved upon modification, but the law requires a *reason* for the starting point.

Petitioner's expert, Dr. Cornish, offers nothing better, effectively parroting the Petition. *See* Ex. 1002 (Cornish Decl.), ¶¶ 139, 144. Neither Petitioner nor its expert provides any discussion of any other potential lead compounds or explains why a skilled artisan would have selected their proposed lead compound over others in the prior art.

While the Petition pretends otherwise, the reason for Petitioner's focus on Alsina-Fernandez's SEQ ID NO:1, to the exclusion of any other potential lead compounds, is clear. Petitioner is engaged in a classic hindsight-driven selection of a lead compound based on "mere structural similarity" to the claimed compounds. *See Otsuka*, 678 F.3d at 1292, 1296 (affirming the district court's "careful analysis [that] exposed the Defendants' obviousness case for what it was—a poster child for impermissible hindsight reasoning"). The law, however, is clear that this is

improper: "proving a reason to select a compound as a lead compound depends on more than just structural similarity, but also knowledge in the art of the functional properties and limitations of the prior art compounds." *Daiichi*, 619 F.3d at 1354. Petitioner's motivation to select its proposed lead compound comes from one and only one place: the challenged claims themselves.

The only "functional properties" of Alsina-Fernandez's SEQ ID NO:1 that Petitioner even mentions are GIP/GLP-1 dual agonism and half-life. Pet. 17, 26. But Alsina-Fernandez and Just together disclose billions of GIP/GLP-1 dual agonist compounds, including over 50 tested *in vitro* and several tested in animals. Alsina-Fernandez, Tables 4-9; Just, Tables 3-4, Figs. 1-7. And another prior art reference cited by Petitioner, Finan, discloses even more GIP/GLP-1 dual agonists with *in vitro* and *in vivo* data—including ***human*** clinical trial data for one of the compounds. Ex. 1061 (Finan), 10-12. The Board has found human clinical studies "particularly relevant" to lead compound selection. *See, e.g.*, *Mylan Pharms.*, IPR2023-00722, Paper 9 at 28 (finding "particularly relevant the status of clinical investigations for GLP-1 analogs as of the [patent's] filing date"); *Mylan Pharms., Inc. v. AstraZeneca AB*, IPR2015-01340, Paper 79 at 19 (P.T.A.B. Aug. 18, 2017) (finding the prior art compounds "that had advanced to clinical trials for evaluation in humans … were recognized in the art as the most promising"). Yet Petitioner provides no reason for ignoring a GIP/GLP-1 dual agonist that had advanced to clinical testing despite that

fact being "particularly relevant" to the lead compound analysis. Moreover, Alsina-Fernandez does not report any pharmacokinetic results for its compounds (such as half-life), whereas both Just and Finan do. Just, 71 (Example 3); Ex. 1061 (Finan), 14-16; *see Daiichi*, 619 F.3d at 1353-54 (finding no motivation to select the proposed lead compound "over other [prior art] compounds" that "had been ***more thoroughly studied*** than" the proposed lead compound). Petitioner's lead compound selection, then, makes no sense when it could have simply chosen compounds from Just or Finan as a starting point and obviated the need for guesswork—unless driven by hindsight knowledge of the challenged claims.

Moreover, while Petitioner asserts that a fatty acid side chain and exenatide C-terminal motif confer obvious "benefits" as compared to the C-terminal tail of the lead compound (Pet. 26-28, 45-46), several GIP/GLP-1 dual agonists in the prior art already included a fatty acid side chain and exenatide C-terminal motif. *See, e.g.*, Just, 66-67 (compounds 32, 33, 35, 36, 53, 54). Thus, by Petitioner's own logic, a skilled artisan would have been motivated to choose one of those GIP/GLP-1 agonists as the lead compound. Petitioner's selection of Alsina-Fernandez's SEQ ID NO:1 as the lead compound, therefore, exposes the hindsight in Petitioner's choice.

In short, Petitioner provides no explanation for why a skilled artisan would have selected its lead compound over the many other GIP/GLP-1 dual agonists in

the prior art. This omission is fatal, and Petitioner cannot rely on subsequent briefing to remedy it. *See Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369 (Fed. Cir. 2016) ("It is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify 'with particularity' the 'evidence that supports the grounds for the challenge to each claim.'" (quoting 35 U.S.C. § 312(a)(3))). Because Petitioner failed to identify the evidence and arguments necessary to support its lead compound selection, Petitioner's obviousness argument fails as a matter of law.

B. Petitioner Fails To Establish Motivation To Modify The Lead Compound In The Ways Required To Create The Claimed Compounds

Even if one were to accept Petitioner's lead compound selection, its obviousness theory still fails. To begin with, Petitioner has failed to establish a motivation to make any—much less all—of its proposed changes. Petitioner fails to account for the unpredictability of the newly emerging field of GIP/GLP-1 dual agonists (*infra* Section IV.B.1.a), and its purported motivations are grounded in hindsight, not any reasonable perspective of a skilled artisan as of the 2015 priority date.

While not always clear, Petitioner's motivation arguments appear to boil down to what it characterizes as "three" proposed modifications to its lead compound. First, according to Petitioner, a skilled artisan would have replaced 14

C-terminal amino acids of the lead compound with an exenatide-based motif. Pet. 26-40. Second, a skilled artisan would have replaced the arginine at position 20 with lysine and used it as the location to add an albumin-binding moiety to the molecule. *Id.* 40-43. Third, a skilled artisan would have selected a particular albumin-binding moiety disclosed in Lau for addition at Lys^{20}, abandoning the PEGylation strategy used in both Petitioner's lead compound and the only GIP/GLP-1 dual agonist with a publicly known structure to have advanced into human clinical trials by 2015. *Id.* 43-47; Ex. 1061 (Finan) (compound 21); Ex. 2066 (Lorenz 2013), 4016 (MAR701). Petitioner fails to establish that a skilled artisan would have been motivated—without the challenged patent in hand—to make ***any*** of these changes.

Petitioner's characterization of the skilled artisan's path from the lead compound to the claimed compounds as a simple three-step process is fundamentally flawed. Far from disclosing a handful of "straightforward" choices among "known" elements and techniques (Pet. 1, 75-78), the prior art would have presented a skilled artisan with countless alternatives, necessitating dozens of decisions from a wide range of options in modifying the lead compound in a highly unpredictable art. *Infra* Section IV.B.1.a. Rather than three changes, Petitioner's proposal at best constitutes three ***categories*** of changes, each encompassing a large number of options and decision points. Petitioner's hindsight-based approach focuses only on those

specific changes needed to arrive at the claimed compounds, while ignoring the universe of other options a skilled artisan would have considered.

1. No Motivation To Substitute An Exenatide C-Terminal Motif Into The Lead Compound

Petitioner's "first" proposed modification is to substitute an exenatide C-terminal motif in place of the lead compound's C-terminal sequence. Pet. 26-40. Petitioner's characterization of this modification as a single change dramatically oversimplifies it. Petitioner's modification encompasses multiple options and decision points, none of which Petitioner addresses.

a. No Motivation To Modify The Lead Compound's C-Terminal Backbone

Petitioner fails to establish as a threshold matter that a skilled artisan would have modified the lead compound's C-terminal sequence ***at all***. As Petitioner recognizes, Alsina-Fernandez discloses that "SEQ ID NO:1 has utility as a GIP/GLP-1 dual agonist, including for glycemic control and weight loss." Pet. 25. But in the next breath, Petitioner proposes replacing ***nearly one-third*** of the amino acid backbone of the lead compound. Given the difficulty of developing dual agonists, and the unpredictable effects even seemingly minor changes could have on activity at one or both of the targeted receptors (*infra* Section IV.C), Petitioner has not shown that a skilled artisan would have been motivated to make such a drastic change.

Engineering a GIP/GLP-1 dual agonist requires a chimeric backbone generated from ***two*** molecules—GIP and GLP-1, as illustrated in the table below. Ex. 1002, ¶¶ 94, 111, 146. As the table also shows, the lead compound's C-terminal sequence is based on the native GIP tail, sharing 10 out of 13 C-terminal amino acids.

Compound	Amino Acid Sequence
GIP	YAEGTFISDY SIAMDKIHQQ DFVNWLLAQK GKKNDWKHNI TQ
GLP-1 (7-37)	HAEGTFTSDV SSYLEGQAAK EFIAWLVKGR G
Alsina-Fernandez SEQ ID NO:1	YXEGTFTSDY SIXLDKIAQR AFVQWLIAXK GKKQEWKHQI TQC(PEG20K)C(PEG20K)

13 C-terminal Amino Acids

Indeed, as Petitioner recognizes, the FDA-approved GLP-1 receptor agonists liraglutide and semaglutide ***retain*** the native C-terminal GLP-1 sequence. Pet. 35-36; Ex. 1002, ¶¶ 81, 151-152; Ex. 1071, 1696. This undermines Petitioner's alleged motivation to replace the native GIP tail of the lead compound.

Fundamentally, Petitioner's theory that a skilled artisan would have replaced nearly one-third of the lead compound ignores the challenges and unpredictable effects in attempting to design a single compound with activity at two receptor binding sites (here, the GIP and GLP-1 receptors). *See, e.g.*, Ex. 2059 (Gattrell 2013), 693 (noting that multi-agonist drug candidates for type 2 diabetes rarely progress into clinical trials or receive market approval because "[multi-agonist] drug discovery is challenging, and perceived by some to be ***almost impossible***," in large part because "[multi-agonists] need to be optimized against multiple biological targets, [which] poses additional hurdles" compared to design of ***monoagonists***).

Even developing GLP-1 monoagonists yielded unpredictable variation in efficacy and side effect profiles. For example, "liraglutide was associated with fewer side effects than … exenatide," despite both being GLP-1 monoagonists. Ex. 2061 (Timofte 2013), Abstract. And taspoglutide, despite showing greater "head-to-head" efficacy in reducing $HbA1_c$ over exenatide, was discontinued due to "[a]n ***unexpectedly*** high number of adverse events in Phase 3 trials." Ex. 2062 (Kueh 2014), 394. Notably, taspoglutide and liraglutide differ by only four amino acids, yet liraglutide is a therapeutically effective, FDA-approved drug while taspoglutide caused intractable adverse effects that ended its development. Ex. 1013, 1; Ex. 2062 (Kueh 2014), 394.

Compound	Amino Acid Sequence
Liraglutide	HAEGTFTSDVSSYLEGQAAKEFIAWLVRGRG
Taspoglutide	HXEGTFTSDVSSYLEGQAAKEFIAWLVKXR

b. No Motivation To Use An Exenatide C-Terminal Motif

Even if a skilled artisan were motivated to modify the C-terminal backbone, Petitioner fails to show a motivation for adding an exenatide motif to the lead compound, much less the specific sequence it proposes.

Just is the only one of Petitioner's three Ground references that discloses an exenatide motif. Petitioner argues that Just "teaches deleting the amino acid residues at positions 30-42 or substituting with the familiar exenatide C-terminal motif." Pet. 26 (citing Just, [0024], [0025]). In full, Just paragraphs [0024] and [0025] state:

> **[0024]** Without wishing to be bound by any particular theory, 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 a 29 amino acid GIP peptide.
>
> **[0025]** Without wishing to be bound by any particular theory, the addition of Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser, Gly-Pro-Ser-Ser-Gly-Ala-Pro-Pro-Ser, Pro-Ser-Ser-Gly-Ala-Pro-Pro-Pro-Ser or Pro-Ser-Ser-Gly-Ala-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.

These teachings in Just are much too general and equivocal to have motivated a skilled artisan to add an exenatide C-terminal motif to the lead compound. Moreover, the only potential benefit of the exenatide C-terminal motifs taught by Just is that they "may increase GLP1 receptor activity." Just, [0025]. Increased GLP-1 receptor activity, however, would not necessarily have been desirable to a skilled artisan in this case because it could disrupt the lead compound's balanced agonism between the GIP and GLP-1 receptors. Further, the vast majority (46 of 56) of Just's working examples ***do not*** include an exenatide C-terminal motif. *Id.*, 65-67 (Tables 1-2).

Apparently recognizing the weaknesses of Just, Petitioner turns to background references that, according to Petitioner, show "exenatide's C-terminal motif was

associated with reduced clearance mechanisms and increased metabolic stability without unduly sacrificing activity." Pet. 27 (citing Ex. 1048, Ex. 1072, Ex. 1073, Ex. 1074). But Petitioner's background references do not show any such benefits. Exhibit 1048 does not even mention exenatide, much less teach any "clearance" or "metabolic stability" benefits of its C-terminal motif. Exhibit 1072 does not mention those benefits either, instead addressing only the motif's effect on GLP-1 receptor binding affinity. Ex. 1072, 155-57, Fig. 2. And Exhibit 1073 demonstrates that the exenatide C-terminal motif has unpredictable effects. Ex. 1073, Table 2 (showing no statistical difference in half-life between exendin-4 and an exendin-4 analog without its C-terminal motif, Ex(1-30), but increased half-life of a GLP-1 analog with an exenatide C-terminal motif, GLP-Ex, over GLP-1).

Worse yet, Exhibit 1074 actually ***teaches away*** from adding an exenatide C-terminal motif because doing so ***decreases*** GIP binding, which could further risk offsetting the important objective of balanced agonism. Ex. 1074, Table 1; *see* Ex. 1061 (Finan), 4 ("balanced in vitro potency of the [GIP/GLP-1] co-agonist translated to in vivo activity"); *see also Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013) (prior art's "guidance actually teaches away from the Board's posited combination or, at a minimum, provides no evidence of motivation to combine"); *DePuy Spine, Inc. v. Medtronic Sofamor Danek, Inc.*, 567 F.3d 1314,

1327 (Fed. Cir. 2009) (reference teaches away when it "'criticize[s], discredit[s], or otherwise discourage[s]' investigation into the invention claimed").

Finally, as to Petitioner's alleged "low immunogenicity" benefit of the exenatide C-terminal motif (Pet. 15, 78), adding a stretch of exogenous amino acids from a ***third*** molecule, exendin-4—which is endogenous to the Gila monster, not humans—would have only ***increased*** the risk of immunogenicity by Petitioner's own logic. Ex. 1002, ¶¶ 151-152 (opining that an "unnatural sequence was potentially undesirable as it raised the risk of high immunogenicity"); *see also* Ex. 2063 (Knudsen 2000), 1666 (noting that for "analog[s] of a naturally occurring hormone, there is always a risk of introducing a change in the amino acid sequence, which can lead to an immune response"). In fact, when comparing the proportion of patients that exhibited anti-drug antibodies at the end of treatment with exenatide or liraglutide, there was a ***20-fold*** difference between the two, with liraglutide—which does ***not*** have an exenatide C-terminal motif—eliciting anti-drug antibodies in far fewer patients despite a substantially longer duration of treatment. Ex. 1071, 1700. If anything, therefore, Petitioner's cited art suggests that foreign sequences derived from exenatide, such as its C-terminal motif, could ***increase*** the risk of immunogenicity.

c. No Motivation To Replace Aib At Position 29 With Glycine

Petitioner next argues that adding an exenatide C-terminal motif "as a whole beginning at position 29" would "avoid unnecessary use of the non-natural (and potentially immunogenicity-inducing) Aib at position 29 by employing the [glycine] found naturally [at the same position, i.e., 'Gly29'] 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." Pet. 35; *see id.* 76-77. Petitioner fails to show that a skilled artisan would have made this change at all, much less to reduce immunogenicity risk.

Just does not teach substituting an exenatide C-terminal motif to remove the Aib at position 29. Quite the contrary, Just teaches that "truncation [of its dual agonists] can be of any length (1-13 amino acids) down to a ***29*** amino acid GIP peptide," not "down to a ***28*** amino acid peptide." Just, [0024]. Thus, Just expressly teaches that the amino acid at position 29 should be maintained when appending an exenatide C-terminal motif—in other words, that any addition thereof should be at an amino acid residue after position 29. Indeed, ***none*** of Just's working examples substitute an exenatide C-terminal motif starting at position 29. *See id.*, 65-67 (Tables 1-2). Eight of Just's working examples add an exenatide C-terminal motif starting at position 30, and two add it at position 31. *See id.* Petitioner therefore fails to show that Just teaches "truncating the peptide after position 28 or substituting

the C-terminal residues with the familiar exenatide C-terminal motif," which Petitioner asserts in arguing that Just would have motivated a skilled artisan to replace Aib29 with Gly29. Pet. 73.

Petitioner's argument ignores other express teachings of Just as well. For example, Just teaches that Aib29 "***will enhance the stability of the peptide*** towards enzymatic degradation." Just, [0027]. Petitioner fails to explain why a skilled artisan would have desired to replace Aib29 of the lead compound when it could improve stability of the compound. *See Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 296 (Fed. Cir. 1985) (a "reference … must have been considered for ***all*** it taught"). In fact, ***not a single one*** of Just's 56 working examples have glycine at position 29, whereas nearly half of them have Aib at that position. Just, 65-67 (Tables 1-2).

Petitioner argues that a skilled artisan would have substituted Aib29 with a natural amino acid to reduce the risk of immunogenicity, and would have chosen Gly29 because it is found in GLP-1, exenatide, and liraglutide. Pet. 35. But even if a skilled artisan would have substituted a natural amino acid for Aib29, Petitioner fails to explain why she would choose glycine rather than, for example, glutamine ("Gln29"), especially given the only compounds tested *in vivo* in Just also use Gln29, as found in native GIP. Just, 66 (Table 2, compounds 32 and 33), 71-72 (Examples 3-5). Nor does Petitioner explain why a skilled artisan—without the challenged

claims in hand—would select glycine from among the ***six*** natural amino acid options that Just teaches for position 29, where Just provides no preference for one over another. *Id.*, [0007]-[0020].

Furthermore, Petitioner fails to establish that Gly29 would reduce the risk of immunogenicity. Petitioner's cited art does not show that exenatide's C-terminal motif, much less Gly29 specifically, is related to the immunogenicity of the molecule as a whole. Ex. 1053, 9; Ex. 1069, Table 4; Ex. 1070, Abstract; Ex. 1071, Abstract. Nor does Petitioner point to any prior art showing that adding an exenatide motif with a Gly29 ***decreases*** the risk of immunogenicity. And Petitioner ignores that its own cited references teach that exenatide and liraglutide—both of which have Gly29—are themselves immunogenic, inducing hypersensitivity-based "injection-site reactions" as well as formation of anti-exenatide and anti-liraglutide antibodies during the course of treatment. Ex. 1070, Abstract, 551.

d. No Motivation To Select A Particular "Exenatide Motif" From The Many Options In The Prior Art

Petitioner proposes adding amino acids 1-28 of "SEQ ID NO:1 together with the [11-amino acid] exenatide C-terminal GGPSSGAPPPS motif." Pet. 35. But Just does not teach Petitioner's purported 11-amino acid motif as an option, pointing instead to ten-, nine-, and eight-amino acid sequences. Just, [0025]. And Petitioner cites no other prior art reference disclosing an 11-amino acid exenatide motif. Indeed, Petitioner's own cited prior art repeatedly identifies the ***nine***-amino acid

sequence PSSGAPPPS as the canonical exenatide C-terminal motif. Ex. 1072, 153; Ex. 1073, 18. Absent Petitioner's mischaracterization of the exenatide C-terminal motif, there is no reason to select glycine for position 29. Just expressly teaches that Aib29 is preferred, and it teaches ***seven*** amino acid options for position 29, without identifying any benefit of choosing glycine for that position. *Supra* Section IV.B.1.c.

2. No Motivation To Conjugate An Albumin-Binding Moiety To Lysine At Position 20

Petitioner's "second" proposed modification is to use a Lysine at position 20 as the point for conjugation of an albumin-binding moiety to the compound. Pet. 40-43. As with its "first" proposed modification, however, Petitioner's characterization of this "second" modification as one straightforward change is inaccurate. Petitioner's "second" modification encompasses at least two changes: (1) replacing the arginine at position 20 of the lead compound with lysine; and (2) selecting position 20 as the point of attachment for an albumin-binding moiety.

a. No Motivation To Replace Arginine At Position 20 Of The Lead Compound With Lysine

The dual agonists in Alsina-Fernandez, including Petitioner's lead compound, all contain an arginine residue at position 20. And as Petitioner admits, these compounds were shown to have balanced GIP/GLP-1 activity. Pet. 16 (describing Alsina-Fernandez as disclosing "peptides that achieve a favorable balance of both

GLP-1 and GIP agonisms"). Nonetheless, Petitioner contends that a skilled artisan would have replaced arginine at position 20 with lysine. Petitioner identifies no motivation for this substitution. Moreover, more than half of Just's working examples have an arginine at position 20—as in the lead compound—further undermining Petitioner's proposed substitution. Just, 65-67 (Tables 1-2).

In addition, other prior art teaches that a "lipophilic substituent or the spacer may be conjugated" to an arginine in the amino acid backbone of a GIP/GLP-1 dual agonist compound. Ex. 2064 (U.S. Pat. Appl. Publ. 2016/0015788), [0108]. Given that arginine was already known to be suitable for adding a lipophilic functional group, Petitioner fails to establish that a skilled artisan would have been motivated to substitute another amino acid, much less lysine in particular, in place of arginine at position 20.

b. No Motivation To Conjugate An Albumin-Binding Moiety To Lys^{20}

Petitioner argues that Just and Lau "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." Pet. 40. But Petitioner ignores that ***every*** GIP/GLP-1 dual agonist with an albumin-binding moiety disclosed in Just adds the moiety to a lysine residue at ***position 17***, not position 20, and that Lau is directed to monoagonists not dual agonists. Just, 65-67 (Tables 1-2); *see generally* Lau. Petitioner fails to explain a motivation to use Lys^{20} when Lys17 had already been shown to work for dual

agonists. Just, Tables 1-3. Petitioner is also wrong that Just's disclosure of GIP/GLP-1 dual agonists with Lys^{20} supports adding an albumin-binding moiety at position 20. Pet. 40-41; Ex. 1002, ¶ 159. Although some of Just's working examples include Lys^{20}, many more have other amino acids at position 20, and ***none*** have an albumin-binding moiety conjugated at Lys^{20}. Just, 65-67 (Tables 1-2). If anything, Just's disclosure of dual agonists with Lys^{20}, but none having an albumin-binding moiety conjugated there, undermines Petitioner's alleged motivation to use Lys^{20} for that purpose.

Moreover, Petitioner fails to explain why a skilled artisan seeking to develop a dual agonist would have disregarded dual agonist prior art teachings in favor of ***monoagonist*** disclosures such as Lau. The prior art taught that receptor binding can differ greatly between mono and dual agonists, including with respect to steric effects based on ***where*** in the amino acid backbone an albumin-binding moiety is added. *See* Ex. 1025, 1604, 1606; Ex. 1024, 475-77. Lau is thus especially inapposite, as it does not disclose any *in vitro* or *in vivo* results that a skilled artisan could use to understand the structure-function relationship of its disclosed compounds even for designing a monoagonist (much less a dual agonist).

Petitioner also does not explain why skilled artisans would prefer conjugation of a fatty acid at position 20 over the many possible sites taught in its cited prior art. For example, Just and Finan teach positions 16, 17, 19, 20, 24, 27, 28, 30, 32, 40 as

locations for conjugation. *See* Just, [0067]; Ex. 1061 (Finan), Table 1. Here again, Petitioner derives its purported motivation for these combined changes not from the prior art, but from the challenged claims themselves.

3. No Motivation To Combine An Albumin-Binding Moiety From Lau With The Lead Compound

Petitioner's "third" proposed modification is the selection of the particular albumin-binding moiety disclosed in Lau for conjugation to the lead compound. Pet. 43-47. As with its first "two" proposed modifications, Petitioner's "third" modification encompasses not a single change, but rather multiple options and necessary decisions. *Infra* Section IV.B.4.

a. No Motivation To Abandon PEGylation For Time Extension And Use Lipidation Instead

Petitioner contends that a skilled artisan would have been motivated to "employ the prior art albumin-binding moiety" of Lau "to improve protracted duration of action to the peptide," thereby achieving once-weekly dosing. Pet. 45; *see id.* 73, 75-76. But the lead compound already ***had*** a well-established mechanism to increase effective duration of action: PEGylation. Indeed, Alsina-Fernandez's "most preferred" compound (SEQ ID NO:3) is PEGylated—a fact that Petitioner conveniently ignores through its illogical proposal. Alsina-Fernandez, 3:25-31. Petitioner entirely fails to show why a skilled artisan would have abandoned that

proven mechanism in what it selected, among all choices, as its lead compound, and instead attach a lipidated albumin-binding moiety.

According to Petitioner, a skilled artisan would have been motivated to use lipidation, as taught by Just and Lau, instead of PEGylation to extend the half-life of the lead compound. But the Petition's only explanation for abandoning PEGylation appears in a single sentence, supported by a single reference: "Although artisans tried PEGylation for increasing peptide half-life, this often created undesirable immune responses." Pet. 14 (citing Ex. 1002, ¶ 65; Ex. 1022 ("Garay")). Petitioner's expert Dr. Cornish's declaration provides no more. Ex. 1002, ¶ 65 ("This approach was known to result in undesirable immunogenicity." (citing Garay)).

Petitioner's threadbare argument does not withstand scrutiny. As an initial matter, the only GIP/GLP-1 dual agonist that had advanced into human clinical trials by 2015 and that had a publicly known structure was PEGylated, not lipidated. Ex. 2066 (Lorenz 2013), 4016 (MAR701); Ex. 1061 (Finan), 9 (compound 21). A skilled artisan would have had no compelling reason to depart from PEGylation given its use in the only clinically tested dual agonist that a skilled artisan could have referred to for structural guidance before the priority date.

In addition, while Petitioner's single supporting reference, Garay, reports anti-PEG antibodies in humans, it does not suggest abandoning PEGylation of

pharmaceuticals. To the contrary, Garay states that "PEGylation of therapeutic agents have shown, and will continue to show, *great value in medicine* to address toxicity, immunogenicity and rapid clearance of an unconjugated drug while maintaining efficacy in the treatment of many diseases." Garay, 1322. Garay concludes, "it is ***possible*** that a ***subset*** of patients with anti-PEG may not benefit from treatment with PEG-conjugated agents," but that "[f]urther research is warranted to evaluate the therapeutic risk." *Id.* In fact, Garay notes that "at least 12 therapeutic PEGylated agents" had been approved by the time of its publication in 2012 (*id.*, 1319-20), and indeed that number had grown to 38 FDA-approved PEGylated therapeutics by 2024 (Ex. 2065 (Gao), 5). Thus, contrary to Petitioner's argument, the use of PEGylation as a half-life extension strategy was being successfully pursued as of the priority date and still is today.

Petitioner next argues that a skilled artisan would have used lipidation to extend the half-life of the lead compound because it was "[a] common approach to extending duration of action of peptides" and because it was used in the GLP-1 monoagonists liraglutide and semaglutide, and in the GIP/GLP-1 dual agonists disclosed in Just. Pet. 14-15, 45-46. But there were numerous "common approaches" for time extension as of 2015, so the fact that lipidation was one of them does not distinguish it. Ex. 2066 (Lorenz 2013), 4013-16 (describing a "variety of strategies … to provide novel GLP-1 RAs with longer-term in vivo activity,"

including stabilization by amino acid exchange, sustained-release formulations, conjugation to albumin, Fc fusion, coupling to biological polymers, lipidation, and PEGylation).

Petitioner's argument also ignores the unpredictable risks and limitations of lipidation that were known in 2015. For instance, "[l]ipidation can change the secondary structures of peptides through the hydrophobic interactions of the fatty acid chain with the peptide backbone or side chains." Ex. 1025, 1602-03. And this is particularly true for "[l]ong-chain fatty acid (>C_8) lipidations," as in the claimed compounds. *Id.*, 1603.

Accordingly, Petitioner fails to demonstrate that a skilled artisan would have been motivated to abandon PEGylation, as used in Petitioner's lead compound, in favor of lipidation.

b. No Motivation To Use The Particular Albumin-Binding Moiety From Lau

Further, Petitioner relies on inapposite monoagonist teachings in Lau in arguing that a skilled artisan would have been motivated to use the albumin-binding moieties from Lau Examples 4-5, which disclose C18-C20 fatty diacids and a γGlu-AEEA-AEEA spacer. Pet. 44-45. This is both incorrect and hindsight-driven.

Lau is inapposite because it concerns monoagonists, not dual agonists. This is important because Petitioner's own cited art taught that the effect of albumin-binding moieties was unpredictable when applied to dual agonists. Ex. 1024, 472,

475-77 (receptor activity "results highlight the sensitivity of the two receptors to the location and chemical structure in which the lipid is covalently fixed to the peptide" and "[m]ore subtle differences in peptide structure are evidently producing the sizable potency differences in receptor co-agonism").

Further, the prior art actually ***teaches away*** from using the claimed fatty acids for lipidation. Petitioner's own cited prior art suggests that "[l]ong chain fatty acid lipidation can cause considerable decreases in receptor binding affinity as compared to short-chain fatty acid lipidation." Ex. 1025, 1606. For example, while a C4-acylated somatostatin receptor ligand showed 10-fold decrease in receptor affinity over the native ligand, a C18-acylated analog of the same ligand had a 30-fold decrease in receptor affinity. *Id.*

Petitioner's cited art also discloses millions of different fatty acid options for lipidation of GIP/GLP-1 dual agonists. Just alone teaches a fatty acid component of an albumin-binding moiety can be anywhere from ten to 24 carbon atoms, branched or unsaturated at ***any*** position along the carbon chain, or substituted with one of a number of different functional groups. Just, [0061]-[0062]. Petitioner fails to explain how it navigated this sea of options to arrive at the claimed fatty acids.

Furthermore, Petitioner's cited art discloses lipidated GIP/GLP-1 dual agonists having a wide variety of possible spacers, as well as dual agonists that do not contain a spacer and instead are conjugated directly. *See Id.*, [0064]; Ex. 1061

(Finan), Table 1 (compounds 7, 19). In fact, the two GIP/GLP-1 dual agonists that Just tested *in vivo* have an isoGlu spacer, which lacks the AEEA-AEEA components of the spacer from Lau Examples 4-5. *Compare* Just, 66 (compounds 32 and 33), *with* Lau, 47-48 (Examples 4-5). In view of these GIP/GLP-1 dual agonist teachings with different spacers than Lau's, Petitioner's argument that a skilled artisan would have chosen the particular spacer used in Lau's inapposite monoagonists only further exposes Petitioner's hindsight.

Finally, Petitioner fails to address the potentially undesirable effects on receptor binding due to the choice of fatty acid and anchor position: "[t]he anchor positions and the chain lengths of fatty acids have great influence on the receptor binding ability of lipidated peptides." Ex. 1025, 1606. In particular, "[l]ong-chain fatty acid lipidation can cause considerable decreases in peptide receptor binding affinity as compared to short-chain fatty acid lipidation." *Id.*

Therefore, Petitioner fails to show that a skilled artisan would have been motivated to use the specific albumin-binding moieties disclosed in Examples 4-5 of Lau to modify its lead compound.

4. Petitioner Ignores An Immense Number Of Alternative Options And Decisions Underlying Its Proposed Modifications

To cap off its motivation arguments, Petitioner contends in a single paragraph that the claimed invention would have been "obvious to try from among a finite

number of identified, predictable solutions." Pet. 77-78. In particular, Petitioner argues that its proposed combination merely "substitutes one known element for another" and "uses a known technique" to "improve a similar product in the same way to yield predictable results." *Id.* But Petitioner's own cited references demonstrate that a skilled artisan would have faced an extraordinary number of alternative options and decision points at every turn, resulting in countless possibilities, all of which could have unpredictable results.

Petitioner's "obvious to try" argument relies on a single paragraph from its expert's declaration that parrots conclusory attorney argument. Ex. 1002, ¶ 140. The Board has denied institution in similar circumstances where the petition lacked credible evidence to support an obvious to try theory. *See, e.g.*, *Current Lighting Sols., LLC v. Jiaxing Super Lighting Elec. Appliance Co.*, IPR2023-00269, 2023 WL 5319763, at *11 (P.T.A.B. Aug. 16, 2023) ("Petitioner d[id] not provide persuasive support for its conclusory assertion of a finite number of identified, predictable solutions"); *Fujian Sanan Grp. Co. v. Epistar Corp.*, IPR2018-00963, 2018 WL 6131939, at *8 (P.T.A.B. Nov. 20, 2018) ("[a]part from attorney argument, [petitioner] d[id] not present credible evidence to support its assertion that one of ordinary skill in the art would have understood that there are a limited number of possibilities").

Multiple decision points underly each of Petitioner's proposed modifications, none of which Petitioner addresses. For example, even assuming there was a motivation to modify the C-terminal backbone, a skilled artisan would need to make several decisions to arrive at the precise modification Petitioner advances, including: (1) deciding to add a C-terminal motif from exenatide; (2) deciding where in the amino acid backbone the exenatide C-terminal motif should be substituted; and (3) selecting the specific exenatide C-terminal motif from among the options disclosed in the prior art.

Petitioner likewise fails to address the decisions a skilled artisan would have needed to consider when deciding whether to conjugate an albumin-binding moiety, including: (1) abandoning PEGylation, the modality for time extension used for Petitioner's lead compound; (2) choosing lipidation for extending duration of action (over other strategies in the prior art); (3) choosing the carbon chain length of the fatty acid; (4) deciding whether to use a fatty mono- or di-acid; (5) deciding on the fatty acid's structure (e.g., linear, branched, saturated, unsaturated); (6) deciding whether to conjugate the fatty acid directly to the amino acid backbone or use a spacer; (7) choosing the specific position in the backbone for conjugation; (8) choosing the specific amino acid type to which the albumin-binding moiety is conjugated; and (9) choosing the specific spacer molecule.

Collectively, the multitude of decision points and corresponding options yield an immense number of disparate compounds; there were not a "finite number of identified, predictable solutions" leading to the claimed compounds. *See Leo Pharm.*, 726 F.3d at 1356 (claims not obvious to try in view of "the breadth of the[] choices and the numerous combinations" disclosed); *Par Pharm., Inc. v. Novartis AG*, IPR2016-00084, 2018 WL 389192, at *15 (P.T.A.B. Jan. 11, 2018) (skilled artisans "would have been faced with a large number of decision points" and "[o]nly by making the 'right' choice at each step would the skilled artisan arrive at" the claims). Petitioner's only roadmap through these choices is the patent itself.

C. Petitioner Fails To Establish A Reasonable Expectation Of Success In Modifying The Lead Compound To Create The Claimed Compounds

Even if Petitioner had shown a motivation to make each and every one of the changes to the lead compound that would have been required to create the claimed compounds, Petitioner fails to establish a reasonable expectation of success in doing so. Institution should be denied on this independent basis.

As an initial matter, Petitioner's purported reasonable expectation analysis largely parrots its arguments that a skilled artisan would have had "good reason" to make the proposed modifications (indeed, it is often hard to tell which one Petitioner is arguing at any given point). But these are distinct inquiries. Petitioner cannot establish reasonable expectation of success by reiterating its motivation theories.

See Eli Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1344 (Fed. Cir. 2021) ("[W]e must first emphasize the clear distinction in our case law between a patent challenger's burden to prove that a skilled artisan would have been motivated to combine prior art references and the additional requirement that the patent challenger also prove that the skilled artisan would have had a reasonable expectation of successfully achieving the claimed invention from the combination."), *appeal dismissed sub nom. Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, No. 2024-1094, 2025 WL 2590270 (Fed. Cir. Sept. 8, 2025).

Another theme of Petitioner's arguments is the complete disregard for the well-established unpredictability associated with engineering pharmaceutical compounds generally, and highly complex molecules such as dual agonists in particular. *See supra* Section IV.B.1.a. For instance, Finan describes the steep "synthetic challenge in identifying ***single*** peptides of optimal ***balance***" in GIP/GLP-1 dual agonists, noting that "proving their unique pharmacology is often a big technical challenge." Ex. 1061 (Finan), 2; *see also* Ex. 2067 (Teng 2010), 336 ("[R]esidue changes at key sites within a protein may result in a series of conformation changes," which may "cause protein aggregation and destabilization" and "affect protein-protein interactions," such as receptor binding.); Ex. 2059 (Gattrell), 693 ("[Multi-agonist] drug discovery is challenging, and perceived by some to be almost impossible.").

As explained below, Petitioner fails to establish a reasonable expectation of success in making ***any*** of the required modifications to its lead compound separately, let alone a reasonable expectation of success in making ***all*** of the required modifications ***together***.

1. No Reasonable Expectation Of Success In Substituting An Exenatide C-Terminal Motif Into The Lead Compound

Petitioner argues that "a POSA would have had a reasonable expectation that" a compound resulting from "substituting exenatide's C-terminal motif in place of the foreign C-terminal motif employed in SEQ ID NO:1" of Alsina-Fernandez "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 [Alsina-Fernandez and Just]." Pet. 27-28. Relying on the GIP and GLP-1 *in vitro* assay data presented in Just (some of which the Petition reproduces in Tables A and B at pages 29-30), Petitioner argues that "employing the exenatide C-terminal motif was very compatible with effective dual agonism." *Id.* 28. Further, according to Petitioner, "[t]he *in vivo* data in [Just] likewise indicated the exenatide C-terminal motif resulted in favorable efficacy." *Id.* 31.

But Petitioner fails to demonstrate that the data in Just supports a reasonable expectation of success. First of all, Petitioner points to nothing in Just's *in vitro* data indicating that the exenatide C-terminal motif itself either helps or hinders "effective dual agonism." As shown in Petitioner's Tables A and B, Just's compounds with an

exenatide C-terminal motif are all over the map: some are near the top in GIP activity (Table A), while others have much lower activity than compounds lacking the motif; likewise, some are near the top in GLP-1 activity (Table B), while others have much lower activity than compounds lacking the motif. *Id.* 29-30. Moreover, Petitioner does not point to any of Just's compounds as showing activity at ***both*** receptors (i.e., "effective dual agonism").

Similarly, Petitioner identifies nothing in Just's *in vivo* data indicating that adding the exenatide C-terminal motif itself "resulted in favorable efficacy," as Petitioner argues. *Id.* 31. As noted above, Just tested only two compounds *in vivo*—nos. 32 and 33—both of which have an exenatide C-terminal motif. *Id*. Just did not test any of its own compounds lacking a C-terminal motif *in vivo*. In other words, there was no appropriate "negative control" in Just's *in vivo* experiments, and therefore no way of knowing whether or not "the exenatide C-terminal motif resulted in favorable efficacy." Petitioner's arguments on this point are, therefore, completely unsupported.

Even if Petitioner had shown that the exenatide C-terminal motif was responsible for (or even compatible with) any activity of Just's compounds, Petitioner still has not shown that a skilled artisan would have reasonably expected that the combination of ***Petitioner's lead compound*** and an exenatide C-terminal motif from Just "would function well as a GIP/GLP-1 receptor dual agonist," as

Petitioner claims. *Id.* 28. In particular, Petitioner argues that a skilled artisan would have had a reasonable expectation of success in "employing residues 1-28 of [Alsina-Fernandez's] SEQ ID NO:1 together with" an exenatide C-terminal motif from Just. *Id.* 35. As the following table shows, however, Just's compounds with an exenatide C-terminal motif differ from the lead compound in at least ***three positions*** (and as many as nine positions) over residues 1-28:

Compound	Amino Acid Sequence
Alsina-Fernandez SEQ ID NO:1	YXEGTFTSDY SIXLDKIAQR AFVQWLIAXK GKKQEWKHQI TQ
Just 2	YXEGTFTSDY SIXLDKKAQR AFVEWLLAQG PSSGAPPPS
Just 28	YXEGTFTSDY SIYLDKKAQR AFVNWLLAXG PSSGAPPPS
Just 29	YXEGTFTSDY SIYLDKKAQR AFVNWLLAXG PSSGAPPS
Just 32	YXEGTFTSDY SIXLDKKAQR AFVEWLLAQG PSSGAPPPS
Just 33	YXEGTFTSDY SIYLDKKAQR AFVEWLLAQG PSSGAPPPS
Just 35	YXEGTFTSDY SIYLDKKAQR AFVNWLLAXK PSSGAPPPS
Just 36	YXEGTFTSDY SIALDKKAQR AFVNWLVAXK PSSGAPPPS
Just 53	YXEGTFTSDY SIYLDSKAAH DFVEWLLSAG PSSGAPPPS
Just 54	YXEGTFTSDY SIYLEKKAAK EFVEWLLSAG PSSGAPPPS
Just 55	YXEGTFTSDY SIYLDSKAAH DFVEWLLSAG PSSGAPPPS

Alsina-Fernandez, 2:12-25; Just, 65-67 (Tables 1-2). Due to the unpredictability of amino acid substitution on protein structure and function, Petitioner fails to show that merely because an exenatide C-terminal motif may have been compatible with some of Just's compounds, a skilled artisan would have expected the motif to be

successfully compatible with a distinct compound that differs in anywhere from three to nine amino acid positions.

Nor has Petitioner shown a reasonable expectation of success in replacing Aib at position 29 of the lead compound with glycine. Petitioner argues that this substitution "would avoid unnecessary use of the non-natural (and potentially immunogenicity-inducing) Aib at position 29" (Pet. 35), but Petitioner does not explain why a skilled artisan would have reasonably expected that the lead compound, with an Aib29 to Gly29 substitution, would retain balanced activity (or any activity at all) at the GIP and GLP-1 receptors. The Petition is entirely devoid of such an explanation. Petitioner, therefore, has not shown a reasonable expectation of success in making this substitution.

2. No Reasonable Expectation Of Success In Conjugating An Albumin-Binding Moiety To Lysine At Position 20

Petitioner argues: "In view of common prior art usage of Lys^{20} for conjugation, including the disclosures of [Lau] and [Just], 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" Petitioner's lead compound. Pet. 41. But as with the Aib29 to Gly29 substitution discussed above, Petitioner fails to explain why a skilled artisan would have reasonably expected that the lead compound would retain dual GIP/GLP-1 activity

if the arginine at position 20 had been replaced with lysine. This failure alone sinks Petitioner's obviousness argument.

Moreover, Petitioner does not identify any suggestion in the prior art that conjugation of an albumin-binding moiety at position 20 would be successful for a GIP/GLP-1 ***dual agonist***. Instead, Petitioner argues simply that conjugation at position 20 worked for GLP-1 ***monoagonists*** disclosed by Lau and would therefore also work for GIP/GLP-1 dual agonists. *Id.* 40-41. But Petitioner fails to explain how a monoagonist conjugation position can be cross-applied to dual agonists despite significant differences in the amino acid backbones and the additional requirement for binding to ***two*** different receptors (with likely differences in conformational features that would be unpredictably affected by lipidation). For example, even for GLP-1 monoagonists, the prior art teaches that changes in lipidation position can unpredictably affect potency. Ex. 1025, 1606 ("The anchor positions and the chain lengths of fatty acids have great influence on the receptor binding ability of lipidated peptides."). Thus, due to the unpredictable effects on dual agonism, Petitioner has not shown that a skilled artisan would have reasonably expected success in conjugating an albumin-binding moiety at Lys^{20} of the lead compound.

3. No Reasonable Expectation Of Success In Combining An Albumin-Binding Moiety From Lau With The Lead Compound

In conclusory fashion (once again), Petitioner contends that a skilled artisan would have 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." Pet. 45-46; *see id*. 73-74.

But Petitioner fails to show a reasonable expectation of success in adding a C12-C22 diacid albumin-binding moiety, via a γGlu-AEEA-AEEA spacer, from Lau (which teaches only monoagonists) to its lead compound (a dual agonist). Indeed, Petitioner's own references emphasize the unpredictability of lipidation: "even subtle changes in lipidation strategy, including the type of fatty acids, lipid anchor position or spacer insertion can produce profound impacts on the physicochemical properties and bioactivities of lipidated peptides." Ex. 1025, 1613. According to the same reference, "[e]xtensive SAR studies are necessary to take full advantage of lipidation to convert peptides into drugs, since mixed results on ADME properties of lipidated peptides emphasize the complexity of this modification strategy." *Id.* Given the unpredictable effects of these modifications—the impact of each change,

and the cumulative effect of each combination of changes—Petitioner has failed to show a reasonable expectation of success.

4. Petitioner Fails To Show A Reasonable Expectation That All Modifications *Together* Would Have Been Successful

Petitioner's analysis is even more flawed because it fails to consider—much less analyze—why a skilled artisan would reasonably expect success when making multiple modifications ***together***, given the unpredictable effect of each modification on the others. Each change risks unpredictable effects on unrelated parts of the compound, which can negatively impact the compound's desired features. But Petitioner never assesses the impact of making one change on the ability to make any other changes. *See Mylan Pharms.*, IPR2015-01340, Paper 79 at 45 (petition "d[id] not sufficiently take into account the reasonable expectation of success in making a subsequent modification ***given the previous modification***"); *Torrent Pharms. Ltd. v. Merck Frosst Canada & Co.*, IPR2014-00559, Paper 8 at 9 (P.T.A.B. Oct. 1, 2014) (petition did not "sufficiently explain[] why one skilled in the art would have selected the claimed substituents at each of the six independent positions ***all at once***" (emphasis in original)).

Given the complicated interactions between amino acid side chains in the backbone, functional groups attached to the backbone, and the chemical environment around the compound, modifications can cause unpredictable effects on other parts of the compound. Petitioner ignores that its own cited prior art

illustrates the unpredictable effects of one modification on others. In Just, for example, adding an albumin-binding moiety to extend duration of action significantly affected potency, **causing a nine to ten fold decrease in *both* GIP and GLP-1 receptor activity**. Just, Table 3 (e.g., comparing compounds 53 and 55). Additionally, an amino acid substitution of a dual agonist compound in Just intended to resist proteolytic degradation by DPP-IV **resulted in a seven-fold decrease in GIP receptor activity**. *Id.*, Table 3 (comparing compounds 5 and 7).

Table 3: EC_{50} average values of the compounds on the GIP-R and GLP1-R compared to control peptides.

Compound No		GIP R (EC_{50} in nM)	GLP1 R (EC_{50} in nM)
hGIP		0.0038	
Exendin-4			0.0043
2		0.0068	0.015
3		0.015	0.022
4		0.022*	2.6
5		0.031	0.023
6		0.27	0.97
7		0.21	0.024
8		0.10	0.029
		***	
53		0.062	0.092
54		0.037	0.033
55		0.0071	0.0087

And modifying ***only*** the spacer of a GLP-1 analog to modulate duration of action also **resulted in a nearly seven-fold decrease in potency**. Ex. 2057 (Knudsen 2001), 680, Table 1 (comparing compounds 5 and 22).

Table I: GLP-1 compounds and their potency measured using the cloned human GLP-1 receptor expressed in baby hamster kidney cells.

Cpd.	Parent peptide	Acyl site	Acyl substituent	Potency (EC_{50}, pM)
1	GLP-1(7-37)	-	None	55 ± 19
2	K8R26,34-GLP-1(7-37)	K8	γ-Glu-C16	1260 ± 210
3	K18R26,34-GLP-1(7-37)	K18	γ-Glu-C16	35.2 ± 6.2
4	K23 R26,34-GLP-1(7-37)	K23	γ-Glu-C16	30.1 ± 3.3
5	R34-GLP-1(7-37)	K26	γ-Glu-C16	61.0 ± 7.1
6	K27R26,34-GLP-1(7-37)	K27	γ-Glu-C16	36.3 ± 0.3
7	R26-GLP-1(7-37)	K34	γ-Glu-C16	121 ± 26
8	K36R26,34-GLP-1(7-36)	K36	γ-Glu-C16	36.4 ± 2.1
9	R26,34-GLP-1(7-38)	K38	γ-Glu-C16	53.0 ± 2.8
14	R34-GLP-1(7-37)	K26	C16-diacid	154 ± 66
15	R34-GLP-1(7-37)	K26	C14-diacid	72 ± 0.7
16	R34-GLP-1(7-37)	K26	γ-Glu-C18	194 ± 24
17	R34-GLP-1(7-37)	K26	γ-Glu-C14	22.0 ± 7.1
18	R34-GLP-1(7-37)	K26	γ-Glu-C12	27.3 ± 8.4
19	Des-amino-H7R34-GLP-1(7-37)	K26	γ-Glu-C16	687 ± 129
20	R34-GLP-1(7-37)	K26	GABA-C16	84.4 ± 22.1
21	R34-GLP-1(7-37)	K26	β-Ala-C16	113 ± 3
22	R34-GLP-1(7-37)	K26	Iso-Nip-C16	410 ± 120

Understanding the impact of each amino acid substitution—and the non-additive effect of the substitution on other modifications to the lead compound—would require extensive SAR studies not available in the prior art, undermining any reasonable expectation of success.

D. Petitioner's Obviousness Challenge Is Contrary To Established Law

Petitioner asks the Board to invalidate the '780 patent claims without identifying a single case applying a lead compound analysis to invalidate a novel pharmaceutical compound, as it proposes the Board should do here. And for good reason—Lilly's research yielded only ***three such cases ever***, and none remotely resemble the facts here. First, in *Bristol-Myers Squibb Co. v. Teva Pharmaceuticals USA, Inc.*, the claimed compound required just one modification from the prior art and patent owner's expert testified in support of the selection of the lead compound

and the proposed modification. 752 F.3d 967, 969-70, 974-75 (Fed. Cir. 2014). Similarly, in two Board decisions, the claimed compound differed from the prior art by only a single isotopic substitution (deuteration), and the prior art taught isotopic substitution of the lead compounds. *Alzheon Inc. v. Risen (Suzhou) Pharma Tech Co.*, IPR2021-00347, Paper 53 at 5, 54, 66 (P.T.A.B. July 12, 2022), *aff'd sub nom. Risen (Suzhou) Pharma Tech Co. v. Alzheon, Inc.*, No. 2022-2232, 2024 WL 1026081 (Fed. Cir. Mar. 11, 2024) (per curiam) (affirming via Rule 36); *Incyte Corp. v. Concert Pharms., Inc.*, IPR2017-01256, Paper 119 at 5-6, 13-14, 23-24 (P.T.A.B. Apr. 8, 2019), *aff'd sub nom. Sun Pharm. Indus., Inc. v. Incyte Corp.*, No. 2019-2011, 2023 WL 5370639 (Fed. Cir. Aug. 22, 2023).

This case is nothing like those. Here, Petitioner provides no analysis supporting its selection of a lead compound. *Supra* Section IV.A. Further, hindsight would have been necessary to make the numerous substantial modifications required to arrive at the claimed compounds. *Supra* Section IV.B. In short, a conclusion of unpatentability in this case would be unprecedented.

More instructive cases include the Board's denials of institution in the two IPRs concerning the semaglutide compound patents. *See Mylan Pharms.*, IPR2023-00722, Paper 9; *Mylan Pharms. Inc. v. Novo Nordisk A/S*, IPR2023-00723, Paper 9 (P.T.A.B. Oct. 2, 2023). In those cases, the Board found that the petitioner had identified a proper lead compound, liraglutide, largely because liraglutide had

successfully completed Phase II clinical trials (in contrast to Petitioner's lead compound, for which Alsina-Fernandez discloses only *in vitro* and preclinical tests). *See, e.g.*, *Mylan Pharms.*, IPR2023-00723, Paper 9 at 23-26. In addition, liraglutide was closer in its structure to semaglutide than Petitioner's lead compound is to the claimed compounds here, such that fewer modifications would have been required to arrive at semaglutide. *See id., e.g.*, at 26-27. But despite the proper selection of a lead compound and the similar structures of the lead and claimed compounds, ***the Board nonetheless denied institution*** because the petitioner failed to demonstrate a motivation to make even the few specific changes to liraglutide required to arrive at semaglutide, and failed to establish that there would have been a reasonable expectation of success in doing so. *See Mylan Pharms.*, IPR2023-00722, Paper 9 at 26-45; *Mylan Pharms.*, IPR2023-00723, Paper 9 at 23-42.

Here, as explained above, Petitioner fails to establish that a skilled artisan would have selected its lead compound over other prior art compounds. *Supra* Section IV.A. Further, Petitioner fails to establish a motivation to modify the lead compound to arrive at the claimed compounds or a reasonable expectation of success in doing so. *Supra* Section IV.B-C. Petitioner therefore does not even come close to showing a reasonable likelihood that the claimed compounds were obvious.

E. Objective Indicia Confirm Non-Obviousness

Objective indicia of non-obviousness constitute "independent evidence of nonobviousness," and "must be considered." *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1378-79 (Fed. Cir. 2012). The objective evidence here establishes that tirzepatide (1) succeeded where others failed in developing an FDA-approved GIP/GLP-1 dual agonist; (2) satisfied a long-felt, unmet need; (3) has received vast industry praise; (4) is a commercial success; (5) achieved unexpected results; and (6) has been copied.

Lilly is entitled to a presumption of nexus because the "objective evidence is tied to a specific product and that product is the invention disclosed and claimed in the patent." *Immunex Corp. v. Sandoz Inc.*, 964 F.3d 1049, 1067 (Fed. Cir. 2020) (nexus presumed for claims "directed to the active [pharmaceutical] ingredient"); *Teva Pharms. Int'l GmbH v. Eli Lilly & Co.*, 8 F.4th 1349, 1362 (Fed. Cir. 2021) ("[I]t is hard not to imagine a presumption of nexus between a structurally claimed genus of chemical compounds and a commercial product that meets each claim limitation."). The challenged claims cover tirzepatide, the active ingredient in Mounjaro® and Zepbound®. *Supra* Section II.A; Ex. 2073 (Mounjaro® Label (May 2025)), 1, 9-10; Ex. 2074 (Zepbound® Label (Feb. 2025)), 1, 11. Thus, there is a nexus between the objective indicia related to Lilly's FDA-approved products and the claimed invention, such that Lilly's objective evidence should be "accorded

substantial weight." *Wilson Elecs., LLC v. Cellphone-Mate, Inc.*, IPR2018-01774, Paper 10 at 21 (P.T.A.B. Apr. 18, 2019).

While Petitioner asserts that it is unaware of any objective indicia of non-obviousness (Pet. 78-80), its statements and actions prove otherwise. For instance, Petitioner copied tirzepatide because of tirzepatide's commercial success and, in promoting its copies, describes tirzepatide as "novel" and "advancing beyond traditional GLP-1 therapy." Ex. 2075 (Empower Website), 2. Petitioner's own actions and statements establish multiple objective indicia that support non-obviousness, further supporting denial of the Petition. *See Wilson Elecs.*, IPR2018-01774, Paper 10 at 28 (objective indicia "further undermin[ed] Petitioner's [obviousness] challenge").

Failure of Others. Others' failures to develop an FDA-approved GIP/GLP-1 dual agonist further establish non-obviousness. Failure to obtain FDA approval is an appropriate benchmark for failure of others. *See, e.g.*, *Knoll Pharm. Co. v. Teva Pharms. USA, Inc.*, 367 F.3d 1381, 1385 (Fed. Cir. 2004) (per curiam); *Mylan Pharms.*, IPR2015-01340, Paper 79 at 48-49. To this day—more than ***ten years after the priority date*** of the challenged patent—tirzepatide is the ***only GIP/GLP-1 dual agonist*** to have received FDA approval, despite numerous attempts by others. For instance, Just discloses billions of GIP/GLP-1 dual agonists and embodies Zealand Pharma's extensive, but ultimately unsuccessful, efforts. Likewise, Finan

describes failed attempts by Marcadia, Roche, and Novo Nordisk. *Supra* Section II.A.

Long-Felt Need. At the time of Lilly's invention, the available treatment options for diabetes and obesity faced tolerability and efficacy issues, and thus, a need persisted for improved options. *See* '780 Patent, 1:36-39, 2:12-16. Tirzepatide satisfied this need by providing "unprecedented efficacy for glucose lowering and weight loss" while maintaining tolerability. Ex. 2076 (Willard 2020), 1; *see* Ex. 2014, 13. Indeed, the FDA touted tirzepatide as a "first-in-class medicine" that constitutes "***an important advance*** in the treatment of type 2 diabetes" and "***addresses an unmet medical need***" for "both obesity and overweight [conditions]." Ex. 2077 (Mounjaro FDA Approval), 1; Ex. 2078 (Zepbound FDA Approval), 1.

Industry Praise. Tirzepatide and its embodying products, Mounjaro® and Zepbound®, have received extensive industry praise, "weigh[ing] in favor of nonobviousness." *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1334-35 (Fed. Cir. 2016). Petitioner itself praised tirzepatide, stating on its website that "[t]irzepatide brings a novel dual GIP and GLP-1 receptor agonist, advancing beyond traditional GLP-1 therapy." Ex. 2075 (Empower Website), 2. Indeed, tirzepatide has received vast industry acclaim. *E.g.*, Ex. 2025 (N.Y. Times (Apr. 28, 2022)), 2 ("truly going to revolutionize the treatment of obesity"); Ex. 2026 (Medscape (June 4, 2022)), 1

("unprecedented weight-loss achievement"); Ex. 2028 (Bus. Insider (June 6, 2022)), 3 ("very impressive" results).

Tirzepatide also received the highly prestigious Prix Galien Award for "Best Pharmaceutical Product," which is awarded by "Nobel laureates, industry leaders and other highly distinguished individuals in the health sector." Ex. 2079 (PR Newswire (Oct. 27, 2023)), 1-2; Ex. 2080 (Galien Foundation), 4; *see Wilson Elecs.*, IPR2018-01774, Paper 10 at 25 (crediting award given by "unbiased panel of industry leaders").

Commercial Success. Mounjaro® and Zepbound® have also achieved extraordinary commercial success, further contradicting Petitioner's obviousness assertion. *See Crocs, Inc. v. Int'l Trade Comm'n*, 598 F.3d 1294, 1310-11 (Fed. Cir. 2010). Since entering the market in May 2022 and November 2023, Mounjaro® and Zepbound® have generated $26.2 billion and $10.8 billion in worldwide revenue, respectively, through the second quarter of 2025. Ex. 2081 (Lilly 10-K FY 2024), 49, 68; Ex. 2086 (Lilly Press Release: Q2 2025 Earnings Call), 5. The products have captured a significant 57% share of the GLP-1 market, with forecasts projecting that the products will collectively generate $31.1 billion in worldwide sales in 2025 alone. Ex. 2087 (Lilly Presentation: Q2 2025 Earnings Call), 10; Ex. 2082 (Statista 2025).

Unexpected Results. Tirzepatide's unprecedented safety and efficacy likewise support non-obviousness. The inventors discovered that "the length,

composition, and placement of the fatty acid chain and the linker between the peptide and the fatty acid chain [of tirzepatide] ha[d] ***unexpected effects*** …." '780 Patent, 2:6-12; *see* Ex. 2076 (Willard 2020), 1 ("tirzepatide show[ed] ***unprecedented efficacy***"); Ex. 2084 (Sinha 2023), 35, 37 ("***tirzepatide was more efficacious***" and "***largely well tolerated***").

Copying. Petitioner's choice to copy tirzepatide, "rather than [a different product] within the public domain, is probative of nonobviousness because it suggests [Petitioner] saw value in the invention that [it] could not achieve without copying." *Medtronic, Inc. v. Teleflex Innovations S.a.r.l.*, 70 F.4th 1331, 1339 (Fed. Cir. 2023). Petitioner describes itself as "the nation's largest … compounding pharmacy"—its business model therefore foundationally relies on copying. Ex. 2085 (Empower Website – About Us), 2. After knocking off Lilly's patented invention and making millions of dollars by extolling its novelty and virtues, Petitioner should not now be heard to complain that it was not inventive in the first place.

V. CONCLUSION

For the foregoing reasons, Lilly respectfully requests that the Board deny the Petition for *inter partes* review.

Respectfully submitted,

Dated: September 22, 2025

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CERTIFICATE OF COMPLIANCE WITH 37 C.F.R. § 42.24

I hereby certify that this Patent Owner's Preliminary Response complies with the word count limitation of 37 C.F.R. § 42.24(b)(1) because the Patent Owner's Preliminary Response contains a total of 13,425 words, which is the sum of 13,020 words calculated by Microsoft Word's word-count feature and 405 words hand counted in the figures. This total excludes the cover page, signature block, and the parts of the Patent Owner's Preliminary Response exempted by 37 C.F.R. § 42.24(b)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 22nd day of September, 2025, a true and correct copy of the foregoing **Patent Owner's Preliminary Response and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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