

Filed on behalf of: Eli Lilly & Co.

Entered: November 12, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BPI LABS, LLC,
Petitioner,

v.

ELI LILLY & CO.,
Patent Owner.

Case IPR2025-01346
Patent 9,474,780

PATENT OWNER'S PRELIMINARY RESPONSE

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2096	Eli Lilly & Co., Presentation: Q3 2025 Earnings Call (Oct. 30, 2025), https://lilly.gcs-web.com/static-files/81645112-510f-4ce8-a860-c74596c1caa2
2097	Elaine Chen, <i>Eli Lilly's Weight Loss and Diabetes Drug Tops Keytruda as World's Best-Selling Medicine</i> , StatNews (Oct. 30, 2025), https://www.statnews.com/2025/10/30/eli-lilly-zepbound-mounjaro-best-selling-obesity-drug/ (last visited Nov. 7, 2025)

Exhibit	Description
2098	Sequence Listing for WO 2010/011439 A2 Publication (DiMarchi) (Ex. 1017)

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 BPI Labs, LLC (“Petitioner” or “BPI”) challenging U.S. Patent No. 9,474,780 (the “’780 patent”). BPI’s Petition recycles a prior IPR petition filed by Empower, which the Deputy Director recently denied based on Lilly’s strong settled expectations and lack of examiner error in allowing the ’780 patent. *Empower Clinic Servs., L.L.C. v. Eli Lilly & Co.*, IPR2025-01024, Paper 15 (P.T.A.B. Oct. 10, 2025). BPI’s Petition—which is so similar to Empower’s that it adopts the same exhibits and exhibit numbers—asserts the same primary reference (Alsina-Fernandez) and one of two secondary references (Lau), merely substituting a third reference (DiMarchi) for Empower’s final reference (Just). As in *Empower*, the Director should deny institution, for at least four reasons.

First, the Petition uses hindsight to select its lead compound without showing—as legally required—why 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. Petitioner attempts to characterize its path from lead compound to claimed invention as involving “two” straightforward changes, 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 two changes badly misses the mark. Empower described essentially the same obviousness theory as requiring “three” changes, which at best were three *categories* of changes and drastically understated the number of decisions and options at each point. Petitioner’s only roadmap to the claimed compounds 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 an effective dual agonist 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 confirm non-obviousness. *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 \$32 billion in projected sales this year alone. *Unexpected results*: Tirzepatide demonstrates superior efficacy and tolerability to prior art compounds.

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 insulintropic 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.

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." *Id.*, 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:

YX₁EGTFTSDYSIX₂LDKIAQKAX₃VQWLIAGGPSSGAPPPS;

wherein

X₁ is Aib;

X₂ is Aib;

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

X₃ is Phe or 1-Nal;

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

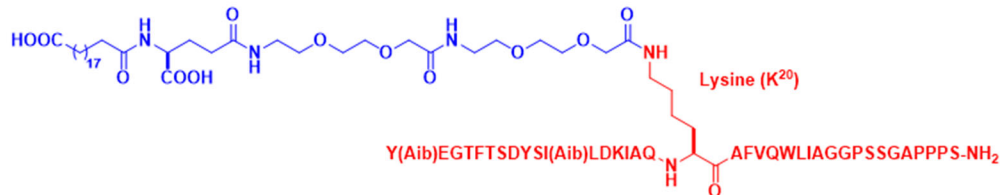
Id., cl. 1. The claim recites a genus of compounds that includes tirzepatide, the active pharmaceutical ingredient in Lilly's groundbreaking Mounjaro[®] and Zepbound[®] products indicated for the treatment of type 2 diabetes (Mounjaro[®]), and obesity and sleep apnea (Zepbound[®]). *Id.*

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 (U.S. Pat. No. 11,357,820), 3:19-33. Tirzepatide has the following sequence:

YX₁EGTFTSDYSIX₂LDKIAQKAFVQWLIAGGPSSGAPPPS

wherein X₁ is Aib; X₂ is Aib; K at position 20 is chemically modified through conjugation to the epsilon-amino group of the K side-chain with $(2\text{-}[2\text{-}(2\text{-Amino-ethoxy})\text{-ethoxy})\text{-acetyl}]_2\text{-(}\gamma\text{Glu)}_1\text{-CO}-(\text{CH}_2)_{18}\text{-CO}_2\text{H}$; 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.

EXAMPLE 2

Alsina-Fernandez, 8:15-22. Petitioner identifies Example 2 as the “lead compound” in its obviousness theory (Pet. 29, 34-42), even though Alsina-Fernandez itself identifies SEQ ID NO: 3 (Examples 4 and 5) as the “most preferred embodiment of the present invention.” Alsina-Fernandez, 3:25-31.

Compound	Amino Acid Sequence & Functional Groups
'780 Patent (SEQ ID NO:3; Tirzepatide)	(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 2010/011439 A2 (DiMarchi) (Ex. 1017)

DiMarchi is a published patent application entitled “GIP-Based Mixed Agonists For Treatment Of Metabolic Disorders And Obesity.” DiMarchi discloses “glucagon peptides that can exhibit potent glucagon activity equivalent to or better than the activity of native glucagon (SEQ ID NO: 1), potent GIP activity equivalent to or better than the activity of native GIP (SEQ ID NO: 4), and/or potent GLP-1 activity equivalent to or better than the activity of native GLP-1.” DiMarchi, 2:9-13. Thus, DiMarchi describes *glucagon* analogs that exhibit GIP, GLP-1, and/or glucagon activity.

Petitioner relies on DiMarchi for the disclosure of multiple limitations of the challenged claims, including an exenatide C-terminal motif¹ and acylation. When accounting for all of the various options described for DiMarchi's “glucagon-based analog[s],” DiMarchi discloses innumerable compounds—at least billions. *See, e.g.*, DiMarchi, 13:15-15:27.

DiMarchi discloses over 250 working examples, fewer than 50 of which are described by DiMarchi as GIP/GLP-1 dual agonists. *See id.*, 124:1-6 (identifying

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. Pet. 19-20.

seven “GLP-1/GIP co-agonist peptides” based on *in vitro* activity at the GIP and GLP-1 receptors), 127:3-5 (identifying one compound (MT251) that “exhibited activity of a GLP-1/GIP co-agonist”), 132:1-10 (noting that, apart from the 35 compounds listed in the first paragraph on page 132, the remaining compounds in Table 3 “exhibited activity at the GIP and GLP-1 receptors”), 143-44 (noting that, in Table 4, “all three acylated dimers demonstrated potent activity at the GLP-1 and GIP receptors”), Tables 1-4. The **vast majority** of DiMarchi's GIP/GLP-1 dual agonists: (1) do not contain a GPSSGAPPPS exenatide C-terminal motif; (2) have Aib at position 20 rather than lysine; and (3) are either not acylated or are acylated without a spacer. Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99, 105. **None** have a fatty acid chain attached at position 20, as required by the claims. *Id.*

DiMarchi discloses *in vitro* data for the compounds it describes as GIP/GLP-1 dual agonists, but it discloses *in vivo* (mouse) data for only eight of those compounds: MT178, MT263, MT274, MT298, MT309, MT311, MT331, and MT353, all of which differ from the claimed compounds in the structure of the albumin-binding moiety (where present), position of conjugation of the albumin-binding moiety, PEGylation (present in seven of the eight compounds), sequence of the C-terminal region, and multiple other amino acids in the backbone. DiMarchi, Figs. 1-38; Ex. 2098, 37, 50-53, 59, 89, 99.

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 DiMarchi, 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, 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 '780 patent claims without any prior art rejections after considering the same or cumulative prior art that Petitioner asserts. *First*, Alsina-Fernandez was cited twice in the specification of the application that issued as the '780 patent. Ex. 1004 (“’780 Patent FH”), 89, 114; '780 Patent, 1:54-56, 20:54-64. In addition, Alsina-Fernandez and the specific amino acid sequence of

Petitioner's lead compound (SEQ ID NO: 5) were referenced in the Examiner's Search Results (Ex. 2088), which Petitioner's file history "Excerpts" ('780 Patent FH) omitted. *Second*, the Examiner reviewed DiMarchi '807 (WO 2010/071807 A1 (Ex. 2089)), which contains materially identical disclosures to Petitioner's DiMarchi reference. '780 Patent FH, 36-37. *Third*, Lau's core disclosure (semaglutide) was referenced **28 times** in the patent's specification, including in *in vivo* testing of semaglutide and the claimed compounds. *See id.*, 90, 98, 115-25. The Search Results referred to semaglutide **12 times** and disclosed structures with the claimed albumin binding moieties more than two dozen times. Ex. 2088, 10, 17, 54, 74-80, 82, 85, 87-92, 95, 99-104, 108, 110-20, 124, 156, 162.

Moreover, the Examiner rejected the same reasoning underlying Petitioner's arguments. In the Reasons for Allowance, the Examiner explained that to make the claimed compounds starting from the reference she found to be the closest prior art, Just (Ex. 1008), 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, the artisan would need "to substitute a Gln at position 24 and a moiety of ([2-(2-Aminoethoxy)-ethoxy]-acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H for the lipophilic substituent, but not make any other changes." *Id.* "There is no teaching or suggestion in Just" for those changes and "[e]ven if there were," making those

changes and no other changes “would *require hindsight reasoning*.”² ’780 Patent FH, 27-28.

IV. PRIOR BOARD PROCEEDING

On May 22, 2025, over two months before BPI filed its Petition, Empower filed a Petition challenging all the claims of the ’780 patent that BPI now challenges, based on two of the same references asserted here. *Empower*, IPR2025-01024, Paper 2 (P.T.A.B. May 22, 2025). Like BPI, Empower asserted one obviousness ground combining Alsina-Fernandez as the primary reference and Lau as one of two secondary references (Empower’s third reference was Just, whereas BPI’s is DiMarchi). And like BPI, Empower limited its lead compound analysis to Alsina-Fernandez, to the exclusion of other GIP/GLP-1 dual agonists known in the art, without explanation or analysis. *Id.*, 26, 76-77. Further, based on an overlapping lead compound theory, Empower suggested that only a handful of modifications were needed to traverse the gap between the lead compound and the claimed compounds (*id.* 26-47), which ignores the reality of the immense number of decision points and options a skilled artisan would have faced.

² Emphases added and internal quotation marks and citations omitted throughout unless otherwise indicated.

In opposing discretionary denial, Empower argued that the Examiner materially erred in purportedly finding that a single amino acid, glutamine at position 24, and an albumin binding moiety were absent from the prior art, and in limiting her analysis to “preferred” disclosures in Just. *Empower*, IPR2025-01024, Paper 11 at 7-9 (P.T.A.B. Sept. 22, 2025). On October 10, 2025, “based on a holistic assessment” of a nearly identical record as here, the Deputy Director denied Empower’s Petition on the ground that the ’780 patent had “been in force for nearly nine years, creating strong settled expectations” for Lilly and that Empower’s “argument that the Office erred during examination of the [’780] patent [wa]s not persuasive.” *Empower*, IPR2025-01024, Paper 15 at 2-3.

V. PETITIONER’S OBVIOUSNESS ARGUMENT FAILS

The Petition asserts that the challenged claims³ would have been obvious but does not come close to establishing a reasonable likelihood of unpatentability. Its

³ 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

sole Ground fails for four independent reasons. The Petition fails to (1) show 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 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 Federal Circuit and the Board have established a specific test to evaluate obviousness challenges to chemical compound patents like the '780 patent—the lead compound test. *See, e.g., Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1290-92 (Fed. Cir. 2012); *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

from which they depend are nonobvious." (quoting *In re Fine*, 837 F.2d 1071, 1076 (Fed. Cir. 1988))).

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.

See Otsuka Pharm., 678 F.3d at 1290-92. The Petition acknowledges the lead compound test but fails to meet it. *See* Pet. 34-35.

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

Though Petitioner admits that GIP/GLP-1 dual agonists “were disclosed in a number of references (e.g., Alsina-Fernandez, DiMarchi, Finan, etc.),” it improperly limits its lead compound selection to the five Examples in Alsina-Fernandez, choosing Example 2 without comparing it to **any** prior art compound from any other reference. Pet. 33-34. In fact, Petitioner’s own asserted reference, DiMarchi, and background references, Finan (Ex. 1061) and Just, collectively disclose **billions** of GIP/GLP-1 dual agonists, including dozens that were tested *in vitro* and/or *in vivo*. But Petitioner ignores them all.

While the Petition pretends otherwise, the reason for Petitioner’s narrow focus on Alsina-Fernandez—and its Example 2—to the exclusion of any other potential lead compounds is clear. Petitioner engages 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 Example 2 that Petitioner even mentions are "promising GIP/GLP-1 dual agonism" and "selectivity over the glucagon [(‘GCG’)] receptor." Pet. 34. But DiMarchi, Finan, and Just disclosed dozens of GIP/GLP-1 dual agonist compounds with those properties, including several tested *in vivo*. In fact, Finan even disclosed **human** clinical trial data for one of its compounds. 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.

Additionally, both Finan and Just disclose half-life values for their *in vivo*-tested GIP/GLP-1 dual agonists. Just, 71 (Example 3); Finan, 9. Petitioner concedes that, by contrast, “half-life values are not reported for the peptides in Alsina-Fernandez,” including Petitioner’s lead compound. Pet. 49; *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.

But even if Petitioner had not improperly limited its analysis to Alsina-Fernandez, its lead compound selection still fails because Petitioner ignores key disclosures that would have led a skilled artisan away from its lead compound. For instance, Petitioner argues that a skilled artisan would have selected Example 2 as a lead compound based on binding affinity data represented by “ K_i values reported in Tables 1 and 2 [of Alsina-Fernandez]” because those values “correlate to ... agonist activity of the GIP and GLP-1 receptors.” Pet. 36-37. In other words, Petitioner

asserts that binding affinity informs the lead compound selection because it is predictive of receptor activity. *See id.* But Alsina-Fernandez teaches **actual** receptor activity data for its compounds, which show that **Example 1** is a more potent agonist of the GIP and GLP-1 receptors than Example 2. *See* Alsina-Fernandez, Tables 4-5. Further, Petitioner's selection of Example 2 directly contradicts Alsina-Fernandez's express teaching that SEQ ID NO: 3 (Examples 4 and 5) is its "most preferred embodiment." *Id.*, 3:25-32; *see Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1379-80 (Fed. Cir. 2006) (flawed lead compound selection dismissed preferred compounds); *Takeda Pharm. Co. v. Torrent Pharms. Ltd.*, No. 17-3186, 2020 WL 549594, at *22 (D.N.J. Feb. 4, 2020) (rejecting lead compound selection where the prior art "contain[ed] a list of 38 preferred compounds, and [the alleged lead compound] [wa]s not on that list"), *aff'd on other grounds*, 844 F. App'x 339 (Fed. Cir. 2021). Petitioner's decision to select a lead compound directly contrary to these teachings exposes the true motivation behind its selection.

Accordingly, Petitioner fails to meet its burden to show "that the skilled artisan would have had a reason to select [its lead compound] from the panoply of known compounds in the prior art." *See Otsuka*, 678 F.3d at 1292.

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 V.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.

Petitioner's motivation arguments appear to boil down to what it characterizes as “two” 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. 42-47. Second, a skilled artisan would have replaced the arginine at position 20 with lysine and selected a particular albumin-binding moiety disclosed in Lau for addition at Lys²⁰, abandoning the PEGylation strategy used in both Petitioner's primary reference and the only GIP/GLP-1 dual agonist with a publicly known structure to have advanced into human clinical trials by 2015. *Id.* 47-65; Finan, 9, Fig. S1 (compound 21); Ex. 1076 (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 two-step process is fundamentally flawed. Far from disclosing a handful of "clear" teachings of prior art choices among "well-known structural substitutions and modifications" (Pet. 26-27, 29), 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 V.B.3. 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. 42-47. 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 teaches its Example 2 has “promising GIP/GLP-1 dual agonism properties, and selectivity over the glucagon receptor.” Pet. 34. But in the next breath, Petitioner proposes replacing *nearly one-third* of the amino acid backbone of the lead compound. *Id.* 42-44. 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 V.B.1.a), 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 incorporating elements from *two* molecules—GIP and GLP-1—as illustrated in the table below. Ex. 1084 ¶¶ 84-88. 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	Y A E G T F I S D Y S I A M D K I H Q Q D F V N W L L A Q K G K K N D W K H N I T Q
GLP-1 (7-37)	H A E G T F T S D V S S Y L E G Q A A K E F I A W L V K G R G
Alsina-Fernandez Example 2 (SEQ ID NO:5)	Y X E G T F T S D Y S I X L D K I A Q R A F V Q W L I A X K G K K Q E W K H Q I T Q 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. 21-22; Ex. 1084 ¶¶ 81-82; 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 HbA_{1c} 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.

DiMarchi is the only one of Petitioner's three Ground references that discloses an exenatide motif. Petitioner argues that "DiMarchi discloses ... attachment of the GPSSGAPPPS tail ... at position 29." Pet. 43 (citing DiMarchi, 5:7-11). In full, DiMarchi states:

"Increased activity at the GLP-1 receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS (SEQ ID NO: 95) or XGPSSGAPPPS (SEQ ID NO: 96) to the C-terminus. GLP-1 activity in such analogs can be further increased by modifying the amino acid at position 18, 28, or 29, or at position 18 and 29, as described herein."

DiMarchi, 5:7-11.

The only potential benefit of the exenatide C-terminal motifs taught by DiMarchi is "[i]ncreased activity at the GLP-1 receptor." *Id.* Increased GLP-1

receptor activity, however, would not necessarily have been desirable to a skilled artisan because it could disrupt the balanced agonism between the GIP and GLP-1 receptors. *See* '780 Patent, 2:27-28 (stating a need for “a balanced co-agonist of GIP and GLP-1 receptors”); Finan, 4 (“balanced in vitro potency of the [GIP/GLP-1] co-agonist translated to in vivo activity”).

Worse yet, Petitioner's Exhibit 1074 *teaches away* from adding an exenatide C-terminal motif because doing so *decreases* GIP binding, which could further risk offsetting the objective of balanced agonism. Ex. 1074, Table 1; *see* Finan, 4; *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”) (original emphasis); *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”).

Petitioner also argues that incorporation of a GPSSGAPPPS tail was a “preferred/prominent design strategy” in DiMarchi because the majority of DiMarchi's “more than 260 exemplary peptide sequences” include the tail. Pet. 46. But fewer than 50 of those exemplary peptide sequences are GIP/GLP-1 dual agonists, the vast majority of which *do not* incorporate a GPSSGAPPPS tail. *See* Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99,

105. Instead, either they have no C-terminal extension or they include an Aib, Cys, or Lys at position 40. *See id.*; DiMarchi, Examples 21, 24, 25. Moreover, as Petitioner acknowledges, “Alsina-Fernandez itself cites ... DiMarchi.” Pet. 42. This undermines Petitioner’s suggestion that a skilled artisan starting with later-published Alsina-Fernandez would have relied on teachings from an older reference that Alsina-Fernandez expressly considered and diverged from in omitting an exenatide C-terminal motif.

Petitioner further argues that the “majority” of Finan’s exemplary peptides disclose a GPSSGAPPPS exenatide C-terminal motif, indicating a “continuing design strategy/motivation.” Pet. 46. But here, too, Petitioner erroneously includes C-terminal motifs used in Finan’s peptides that have a position 40 cysteine or lysine (i.e., GPSSGAPPPSC or GPSSGAPPPSK), which are different than Petitioner’s proposed GPSSGAPPPS motif. Finan, Fig. S1; Pet. 25, 46. In fact, even among the limited subset of Finan’s peptides that had an exenatide C-terminal motif, the majority had motifs with a position 40 cysteine or lysine, not Petitioner’s proposed GPSSGAPPPS motif. Finan, Fig. S1; Pet. 25.

Finally, Petitioner argues that a skilled artisan would have been motivated to use an exenatide motif “to improve [a compound’s] potency and metabolic stability *without inducing undue immunogenicity*.” Pet. 43. But replacing the native GIP-based tail of the lead compound with a stretch of exogenous amino acids from a *third*

molecule, exendin-4—which is endogenous to Gila monsters, not humans—would have only *increased* the risk of immunogenicity by Petitioner's own logic. *Id.* 55 (“preserving native amino acid sequence is generally preferred, as it can help to minimize 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.

Accordingly, Petitioner has failed to demonstrate that a skilled artisan would have been motivated to substitute an exenatide C-terminal motif in place of the lead compound's C-terminal sequence.

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

Petitioner next argues that a skilled artisan would have been motivated to replace Aib at position 29 of the lead compound with glycine. According to Petitioner, DiMarchi teaches “incorporating a glycine (G) residue at position 29, and

connecting the GPSSGAPPPS tail to the glycine at position 29” to (1) increase GLP-1 binding potency, and (2) “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 and synthetic FDA-approved GLP-1 receptor agonists exenatide and liraglutide, as [glycine] at position 29 was known to elicit low-titer anti-drug antibodies consistent with therapeutic efficacy.” Pet. 43-45. Petitioner fails to show that a skilled artisan would have made this change at all, much less to reduce immunogenicity risk.

First, as discussed above, increasing GLP-1 receptor activation would not necessarily have been desirable to a skilled artisan because it could disrupt the balanced agonism between the GIP and GLP-1 receptors. *See supra* Section V.B.1.b. Indeed, DiMarchi’s teachings implicitly acknowledge that increased GLP-1 receptor activation is not always desirable, noting several different ways that “GLP-1 activity may be reduced” in its exemplary peptides, including “deletion of the amino acid at positions 28 and **29**.” DiMarchi, 35:24-31.

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. 44-45. But Petitioner fails to explain why a skilled artisan—without the challenged claims in hand—would select glycine from among the three natural amino acid options that

DiMarchi teaches for position 29, where DiMarchi provides no preference for one over another. DiMarchi, 82:22-23.

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. 1054, 1-2; 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.

Thus, Petitioner has failed to demonstrate that a skilled artisan would have been motivated to replace Aib at position 29 with glycine.

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

Petitioner's “second” proposed modification is to combine a particular albumin-binding moiety from Lau with the lead compound in order to prolong its duration of action. Pet. 47-65. As with Petitioner's “first” proposed modification, however, Petitioner's characterization of this “second” modification as one

straightforward change is a gross oversimplification. Petitioner's "second" modification encompasses at least three changes: (1) replacing the arginine at position 20 of the lead compound with lysine; (2) selecting position 20 as the point of attachment for an albumin-binding moiety; and (3) selecting the particular albumin-binding moiety disclosed in Lau for conjugation to the lead compound.

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

As an initial matter, Petitioner fails to establish a motivation to abandon PEGylation, as taught by Alsina-Fernandez, and use lipidation instead. None of Petitioner's arguments withstand scrutiny.

First, Petitioner argues that a skilled artisan would not have used PEGylation as a time extension strategy because "even the PEGylated peptides of Alsina-Fernandez (which a POSA would know to have longer half-lives because of their PEGylation) were still administered every three days when they were assessed *in vivo*." Pet. 49. But those experiments were conducted in rodents, not humans; and further, Alsina-Fernandez does not disclose any pharmacokinetic information for its compounds. Moreover, Petitioner ignores Finan's disclosure of a PEGylated GIP/GLP-1 dual agonist with a half-life of 120 to 141 hours *in humans*, supporting once-weekly dosing. Finan, 9 (compound 21). In fact, as mentioned above, Finan's compound was the only GIP/GLP-1 dual agonist that had advanced into human clinical trials by 2015 and that had a publicly known structure. Ex. 1076 (Lorenz

2013), 4016 (MAR701). 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.

Second, Petitioner contends a skilled artisan would have been motivated to use lipidation, as taught by DiMarchi and Lau, instead of PEGylation to extend the half-life of the lead compound because “without binding to larger proteins (e.g., serum albumin), small peptides (such as Example 2 in Alsina-Fernandez and exenatide) generally are readily filtered by kidneys from the bloodstream.” Pet. 49. But Petitioner dismisses or ignores many alternative ways of reducing clearance that were known in the prior art—such as PEGylation, slow-release depots, fusion to albumin or the Fc region of IgG, or xtenylation—that focused on modifying pharmacokinetics in ways that did **not** require binding to larger proteins. Ex. 1076 (Lorenz 2013), 4013-16. Indeed, DiMarchi itself teaches that PEGylation is **better** than lipidation at extending duration of action: “[w]hile acylation can extend the half-life of a peptide to hours or more, PEGylation with repeats in tens of kDa ranges can do even more.” DiMarchi, 117:6-7. What’s more, **seven** of the eight *in vivo*-tested DiMarchi GIP/GLP-1 dual agonists are PEGylated, further undermining Petitioner’s argument. Ex. 2098, 37, 50-53, 59, 89, 99. Petitioner asserts the false dichotomy that “without binding to larger proteins,” renal clearance of “small

peptides” is inexorable—revealing its hindsight-informed selection of the *single* time extension strategy used in the claimed compounds, from among myriad options.

Third, in a similar vein, Petitioner argues that a skilled artisan would have used lipidation to extend the half-life of the lead compound because it was “commonly employed to improve metabolic stability, membrane permeability, and bioavailability of peptide drugs,” and because it was used in the GLP-1 monoagonists liraglutide and semaglutide. Pet. 14, 50. But there were numerous approaches for time extension as of 2015; that lipidation was one of them does not distinguish it. Ex. 1076 (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). Additionally, Petitioner fails to explain why a skilled artisan would have set aside *dual agonist* teachings for extending duration of action (PEGylation in Alsina-Fernandez, DiMarchi, and Finan) in favor of monoagonist disclosures for time extension, such as Lau. *See infra* Section V.B.2.c.

Fourth, Petitioner contends that background reference Garay (Ex. 1022) would have led a skilled artisan away from PEGylation due to immunogenicity concerns. Pet. 40-41. But Garay 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.

Finally, Petitioner’s proposed modification 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 (>C₈) lipidations,” as in the claimed compounds. *Id.*, 1603.

Accordingly, Petitioner fails to demonstrate that a skilled artisan would have been motivated to use lipidation over PEGylation.

b. 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, its lead compound was shown to have balanced GIP/GLP-1 activity. Pet. 74 (asserting a skilled artisan "would recognize that the similar binding affinities for GIP and GLP-1 ... represent a 'balanced' co-agonism of GIP and GLP-1"). Nonetheless, Petitioner argues that a skilled artisan would have been "motivated to replace [Arg20] in the Alsina-Fernandez/DiMarchi peptide with [Lys²⁰]" because doing so "was permitted by the teachings of DiMarchi, and the semaglutide compound successfully incorporated this change." *Id.* 55-56.

First, the mere fact that DiMarchi "***permitted***" a lysine at position 20 does not establish a ***motivation*** to replace arginine with lysine in the lead compound. Obviousness requires more than mere feasibility (i.e., that a skilled artisan "could" have modified the prior art). Petitioner must show why a skilled artisan "would" have modified the prior art. *See, e.g., Virtek Vision Int'l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886-87 (Fed. Cir. 2024) ("[O]bviousness concerns whether a skilled artisan not only *could have made* but *would have been motivated to make* the combinations or modifications of prior art to arrive at the claimed invention." (original alteration and emphases)).

In addition, the vast majority of DiMarchi's working examples of GIP/GLP-1 dual agonists have an Aib at position 20, further undermining Petitioner's proposed substitution with lysine. DiMarchi, Tables 1-4; Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99, 105. Moreover, Petitioner acknowledges that DiMarchi teaches Lys²⁰ as one of *seven* possible amino acids at that position, four of which are natural amino acids. Pet. 55; DiMarchi, 40:7-8. And while Petitioner argues that Lys²⁰ would be preferable because native GLP-1 has a lysine at the corresponding position and "preserving native amino acid sequence ... can help to minimize immunogenicity" (Pet. 55), Petitioner then follows with an opposing approach, proposing to delete 14 amino acids (11 of which overlap with native GIP) from the C-terminal end of the alleged lead compound. Petitioner, therefore, does not even adhere to its own proffered design principles.

Furthermore, 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.

c. No Motivation To Conjugate An Albumin-Binding Moiety To Lys²⁰

Petitioner argues that DiMarchi and Lau teach conjugation of the albumin-binding moiety to a lysine at position 20. Pet. 55-56. Specifically, Petitioner argues that DiMarchi “expressly contemplated the attachment of a spacer to the lysine at position 20, similar to the design strategy utilized for semaglutide (as described in Lau).” *Id.* 57. But Petitioner ignores that *every* one of DiMarchi’s GIP/GLP-1 dual agonists with an albumin-binding moiety has the moiety conjugated to a residue at **position 10 or 40**, not position 20, and that Lau discloses only monoagonists, not dual agonists. DiMarchi, Tables 1-4; Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99, 105; *see generally* Lau. Petitioner fails to explain a motivation to use Lys²⁰ as the site for conjugation when DiMarchi had already shown that Lys¹⁰ and Lys⁴⁰ work for dual agonists. DiMarchi, Tables 1-4. Moreover, some of DiMarchi’s GIP/GLP-1 dual agonists have a Lys²⁰, yet **none** of those compounds have an albumin-binding moiety conjugated there, undermining Petitioner’s alleged motivation to use Lys²⁰ for that purpose. Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99, 105.

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. Petitioner presents only a cursory argument that Lau teaches its albumin-binding moiety “is applicable ... to other peptides with

additional modifications to the amino acid sequence but which remain insulintropic agents.” Pet. 52; Lau, 3:8-4:8. But the cited portion of Lau, as relevant here, merely defines the term “insulintropic agent” as a “compound which is an agonist of the human GLP-1 receptor”—there is no mention of a GIP/GLP-1 *dual* agonist. Lau, 3:8-4:8. Even more telling, Lau itself refers to the compounds disclosed by its generic formulas as “GLP-1 analog[s],” not the allegedly broader “insulintropic agents.” *See, e.g., id.*, 12:14, 16:3-19.

In addition, 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, DiMarchi and Finan teach positions 10, 20, 24, 29, 37, 38, 39, 40, 41, 42, and 43 as locations for conjugation via a spacer, and “*any* position within the [dual agonist] peptide ... provided that GIP activity ... is retained.” *See* DiMarchi, 7:17-17, 56:29-57:13, 63:15-18; 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.

Accordingly, Petitioner fails to demonstrate that a skilled artisan would have been motivated to conjugate an albumin-binding moiety to Lys²⁰.

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

Petitioner relies on inapposite monoagonist teachings in Lau to argue that a skilled artisan would have been motivated to use the albumin-binding moieties from Lau Examples 4-6, 10-12, and 15, which disclose C16, C18, and C20 fatty diacids and a γ Glu-AEEA-AEEA spacer. Pet. 57-59. 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").

In addition, Petitioner's cited art discloses millions of different fatty acid options for lipidation of GIP/GLP-1 dual agonists without providing any direction toward the claimed fatty acids in particular. DiMarchi alone teaches a fatty acid

component of an albumin-binding moiety can be anywhere from four to 30 carbon atoms, branched or unsaturated at **any** position along the carbon chain, or substituted with one of a number of different functional groups. DiMarchi, 65:7-14.

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.*, 80:27-81:1 (noting that "[i]n some embodiments, the acyl or alkyl group is **covalently linked** to the side chain of an amino acid"); Finan, Table 1 (compounds 7, 19). In fact, **all** three acylated GIP/GLP-1 dual agonists disclosed by DiMarchi that were tested *in vivo* were conjugated directly without using a spacer. *Compare* Ex. 2098, 51-53, 99 (compounds MT298, MT309, MT353), *with* Lau, 47-48, 50-52 (Examples 4-6, 10-12, 15). In view of these GIP/GLP-1 dual agonist teachings **without** a spacer, Petitioner's argument that a skilled artisan would have used a spacer—much less the particular spacer used in Lau's inapposite monoagonists—only further exposes Petitioner's hindsight.

Finally, 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.*

Therefore, Petitioner fails to show that a skilled artisan would have been motivated to use the specific albumin-binding moieties disclosed in Examples 4-6, 10-12, and 15 of Lau to modify its lead compound.

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

To cap off its motivation arguments, Petitioner contends that “[o]ne basis for obviousness is choosing something from a finite number of identified, predictable solutions, with a reasonable expectation of success.” Pet. 62. In particular, Petitioner argues that “DiMarchi and Lau both teach a small number of fatty acids that may be used as part of the albumin binding moiety.” *Id.* But the prior art did not teach a “finite number of identified, predictable solutions.” In fact, Petitioner’s own cited references demonstrate that a skilled artisan would have faced an extraordinary number of options and decision points at every turn (including for the components of the albumin-binding moiety), resulting in countless possibilities, all of which could have unpredictable results.⁴

⁴ The unpredictability at each step along the path from lead compound to the claimed compounds is detailed in the following section. *See infra* Section V.C.

First, DiMarchi alone discloses billions of potential fatty acids for use in an albumin-binding moiety, which is far from a “small number of fatty acids.” Further, while Petitioner argues it was known “that increasing the length of the fatty acid chain can enhance the half-life of glucagon-like peptide derivatives” (Pet. 62 (referring to Madsen (Ex. 1079))), Petitioner ignores countervailing considerations taught by Madsen itself, such as the loss of potency with increasing fatty acid chain length. Thus, a skilled artisan needed to balance benefits to half-life with detriment to GIP/GLP-1 agonism—hardly a straightforward exercise. *See infra* Section V.B.1.b.

Moreover, multiple decision points underlie 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 multiple 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 by

Alsina-Fernandez; (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 1356-57 (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.

Finally, Petitioner's “obvious to try” argument relies on a single paragraph from its expert's declaration that is ***substantively identical*** to conclusory attorney argument. *Compare* Pet. 62-63, *with* Ex. 1084 ¶ 173. 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) (“Apart 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”).

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 reasonable expectation of success analysis is intermingled with its motivation arguments (indeed, it is often hard to tell which one Petitioner is arguing at any given point). *See, e.g.,* Pet. 46-47 (arguing the alleged “prominence” of the GPSSGAPPPS tail in exemplary prior art peptides supports both motivation to replace the C-terminal residues of the lead compound as well as

reasonable expectation that the replacement would be successful). 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) (noting the “clear distinction” between a patent challenger’s burden on motivation and reasonable expectation of success), *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 of the well-established unpredictability associated with designing novel pharmaceutical compounds generally, and highly complex compounds such as dual agonists in particular. *See supra* Section V.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.” 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 given “the use of the C-terminal GPSSGAPPPS tail across numerous different peptides in DiMarchi, as well as the majority of the exemplary peptides in Finan, a POSA would have reasonably expected that the C-terminal GPSSGAPPPS motif could be successfully utilized in the peptide of Example 2 of Alsina-Fernandez as well.” Pet. 46-47. Further, Petitioner asserts that a skilled artisan would have “reasonably expect[ed] that the exenatide tail would not only enhance the GLP-1 receptor binding activity of the peptide, but would also help to minimize immunogenicity.” *Id.*

But Petitioner fails to demonstrate that the data in DiMarchi supports a reasonable expectation of success when combining the exenatide C-terminal motif with Alsina-Fernandez Example 2. First of all, Petitioner points to nothing in DiMarchi's *in vitro* data indicating that the exenatide C-terminal motif itself either helps or hinders dual agonism—nor can it. As discussed above, only a small minority of DiMarchi's disclosed GIP/GLP-1 dual agonist compounds have the exenatide C-terminal motif proposed by Petitioner, so there is little basis to gauge

whether the motif would be compatible with dual agonism. *See supra* Section V.B.1.b. Moreover, **none** of DiMarchi's disclosed GIP/GLP-1 dual agonists that were tested *in vivo* have the exenatide C-terminal motif proposed by Petitioner. *See supra* Section II.C. The vast majority of the exenatide C-terminal motifs used in DiMarchi's disclosed GIP/GLP-1 dual agonists have an additional amino acid at position 40 and/or 41, such as GPSSGAPPPSC, GPSSGAPPPSK, GPSSGAPPPSAib, and GPSSGAPPPSKC. Ex. 2098, 24-25, 29, 34-35, 37, 43, 45, 50-53, 57-59, 62-65, 71-72, 84, 89-97, 99, 105.

Even if Petitioner had shown that the exenatide C-terminal motif was responsible for (or even compatible with) any activity of DiMarchi'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 DiMarchi would function as a dual agonist. In particular, Petitioner argues that a skilled artisan "would have reasonably expected that the C-terminal GPSSGAPPPS motif could be successfully utilized in the peptide of Example 2 of Alsina-Fernandez." Pet. 47. As the following table shows, however, the limited set of DiMarchi's disclosed GIP/GLP-1 dual agonist compounds with an exenatide C-terminal motif differ from the lead compound in at least ***seven amino acid positions*** (and as many as 10 positions) over residues 1-28:

Compound	Amino Acid Sequence
Alsina-Fernandez Example 2 (SEQ ID NO:5)	YXEGTFTSDY SIXLDKIAQR AFVQWLIAXK GKKQEWHQI TQ
MT148	YSEGTFTSDY SIYLDEQAAK EFWLLAGG PSSGAPPPS
MT149	YAEGTFTSDY SIYLDEQAAK EFVNWLLAGG PSSGAPPPS
MT162	YXQGTFTSDY SYYLDEQAVK EFVNWLIAGG PSSGAPPPS
MT201	YXQGTFTSDY SIYLDEEAVR LFWNWLLAGG PSSGAPPPS
MT268	YXEGTFTSDY SIYLDKQAAK EFWKLLAGG PSSGAPPPS
MT269	YXEGTFTSDK SIYLDKQAAK EFVNWLLAGG PSSGAPPPS
MT270	YXEGTFTSDK SIYLDKQAAK EFVNWLLAGG PSSGAPPPS
MT271	YXEGTFTSDK SIYLDKQAAK EFVNWLLAGG PSSGAPPPS
MT272	YXEGTFTSDK SIYLDKQAAK EFVNWLLAGG PSSGAPPPS
MT337	YXEGTFTSDK SIYLDKQAAK EFVCWLLAGG PSSGAPPPS
MT338	YXEGTFTSDK SIYLDKQAAK EFVCWLLAGG PSSGAPPPS
MT341	YXEGTFTSDK SIYLDKQAAK EFVCWLLAGG PSSGAPPPS

Alsina-Fernandez, 2:12-25; DiMarchi, Tables 1, 3; Ex. 2098, 24-25, 29, 43, 62-65, 93-94, 96. 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 DiMarchi's compounds, a skilled artisan would have expected the motif to be successfully utilized with a distinct compound that differs at anywhere from seven to 10 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. 44), 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 Combining The Albumin-Binding Moiety From Lau With The Lead Compound

Petitioner fails to establish a reasonable expectation of success for either conjugation of an albumin-binding moiety at a lysine at position 20, or use of the specific albumin-binding moiety from Lau.

First, Petitioner argues that a skilled artisan “would reasonably expect that the lysine at position 20 could be successfully acylated.” Pet. 57. 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. Pet. 62-63. But Petitioner fails to explain how a monoagonist conjugation position can be 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 Lys²⁰ of the lead compound.

Second, Petitioner fails to even argue a reasonable expectation of success in adding the *full* C12-C22 diacid albumin-binding moiety, via a γ Glu-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.” *Id.*, 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.

Regarding the fatty acid component of the albumin-binding moiety, Petitioner argues the prior art taught that “increasing the length of the fatty acid chain can enhance the half-life of glucagon-like peptide derivatives.” Pet. 62-63. For support, Petitioner points to Madsen’s disclosure that the increase in half-life of lipidated compounds is directly proportional to an increase of carbon chain length of the fatty acid used in the compound. *Id.* Based on these teachings, Petitioner argues that a skilled artisan would reasonably expect that use of the C16, C18, and C20 fatty acids described in Lau and DiMarchi would “provide a prolonged half-life, similar to what was achieved with the use of a C18 fatty acid in the semaglutide compound.” *Id.* 63.

But Madsen’s teachings are equivocal and do not present a basis for reasonably expecting *any* fatty acid within the challenged claims’ limitations to result in an effective dual agonist. Specifically, Madsen teaches that increasing carbon chain length beyond a C16 fatty acid *negatively* affects potency. Ex. 1079, 6127 (finding that potency of incretin analogs was “negatively effected [*sic*] if the

chain length of the fatty acid was longer than **16** carbon atoms”). DiMarchi corroborates this unpredictability, noting that when testing C14, C16, and C18 acylated peptides, “[a]cylation with a C18 fatty acyl group did not appear to cause a decrease in blood glucose levels, suggesting that the size of the group may be important for glucose lowering effects of the peptides.” DiMarchi, 136:1-5.

Therefore, Petitioner has failed to show a reasonable expectation of success for conjugation of an albumin-binding moiety at a lysine at position 20, or for use of the specific albumin-binding moiety from Lau.

3. 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***” (original emphasis)).

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 prior art that 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.* (comparing compounds 5 and 7).

Table 3: EC₅₀ 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 (annotated below) (comparing compounds 5 and 22).

Table 1: 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 Federal Circuit 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).⁵

⁵ Empower's unsuccessful opposition to discretionary denial raised two other cases, but in one, the Federal Circuit found the lead compound test unnecessary because the art "expressly disclose[d]" the proposed modification (*Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 884-85 (Fed. Cir. 2024)), and in the other, the claimed compound was found **non**obvious on remand (*Altana Pharma AG v. Teva Pharms. USA, Inc.*, No. 04-2355, 2013 WL 12158369, at *1 (D.N.J. Mar. 26, 2013)).

This case is nothing like those. Here, Petitioner provides deficient analysis supporting its selection of a lead compound. *Supra* Section V.A. Further, hindsight would have been necessary to make the numerous substantial modifications required to arrive at the claimed compounds. *Supra* Section V.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* 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 V.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* Sections V.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 extensive industry praise; (4) is a commercial success; and (5) achieved unexpected results.

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).

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 **10 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 (Just, 3:7-16:19, 49:2-52:17) and embodies Zealand Pharma’s extensive, but ultimately unsuccessful, efforts. Likewise, Finan describes failed attempts by Marcadia, Roche, and Novo

Nordisk. Ex. 1076 (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)”).

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). Indeed, tirzepatide has received widespread 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 \$32.7 billion and \$14.3 billion in worldwide revenue, respectively, through the third quarter of 2025. Ex. 2081 (Lilly 10-K FY 2024), 49, 68; Ex. 2095 (Lilly Press Release: Q3 2025 Earnings Call), 3. The products have captured a significant 57.9% share of the incretin analog market, with forecasts projecting that the products will collectively generate \$32.2 billion in worldwide sales in 2025 alone. Ex. 2096 (Lilly Presentation: Q3 2025 Earnings Call), 10; Ex. 2097 (STAT News (Oct. 30, 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, 2:6-11; *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***”).

VI. CONCLUSION

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

Respectfully submitted,

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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 13,392 words, which is the sum of 12,957 words calculated by Microsoft Word's word-count feature and 435 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 12th day of November, 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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