

Filed on behalf of: Eli Lilly & Co.

Entered: August 20, 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 BRIEF ON DISCRETIONARY DENIAL

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I. INTRODUCTION

Patent Owner Eli Lilly & Co. (“Lilly” or “Patent Owner”) respectfully requests that the Director exercise her discretion to deny 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”). Despite Lilly’s long-settled expectations in a patent issued almost a decade ago, Petitioner now seeks a do-over of the examination of the ’780 patent, which protects tirzepatide, the active ingredient of Lilly’s revolutionary drug products for the treatment of diabetes, obesity, and sleep apnea, Mounjaro® and Zepbound®. In doing so, Petitioner asserts the same or cumulative art and arguments that the Examiner already considered and properly rejected. Worse still, it does so in an improper attempt to gain leverage in an unrelated, parallel non-patent litigation between Petitioner and Patent Owner. Discretionary denial is appropriate for at least four reasons, each independently sufficient to deny institution.

First, Lilly’s settled expectations heavily favor discretionary denial. The ’780 patent issued almost nine years ago, in October 2016. It has been in force for years longer than other patents for which the Director has discretionarily denied institution based on the patent owner’s settled expectations. Lilly’s settled expectations are particularly strong here, as Lilly has relied on the patent’s validity in making tremendous investments in researching, developing, and commercializing

Mounjaro[®] and Zepbound[®], both of which embody the claimed invention. Courts and commentators have long recognized that pharmaceutical companies incur extremely high costs in creating new medicines and bringing them to market. And here, Lilly has invested and continues to invest in dozens of clinical trials assessing the safety and efficacy of tirzepatide for numerous potential indications, widely reporting the results in scientific journals and press releases. Following the initial approval of tirzepatide, Lilly commercialized the patented technology and publicly listed the '780 patent in the FDA's Orange Book. Given Lilly's substantial investment in a widely publicized innovation, Petitioner has known, or should have known, of the '780 patent for many years. Petitioner should not be heard to challenge the patent now, nearly a decade into its term, and absent any change in the law to merit its challenge.

Second, the Director should deny the Petition under 35 U.S.C. § 325(d), because Petitioner relies on the same or cumulative prior art to raise substantially the same arguments as those already addressed by the Examiner during prosecution. The Petition's sole Ground relies on three references: Just, Alsina-Fernandez, and Lau. All three are old news. The Examiner not only considered Just, she identified it as the closest prior art to the '780 patent claims and distinguished it in allowing those claims. Alsina-Fernandez was discussed twice in the specification of the '780 patent and was unambiguously before the Examiner. Finally, the core subject matter

of Lau relied on by Petitioner (the compound semaglutide), was referenced *more than two dozen times* in the specification and Lau's other teachings are cumulative of those in Just.

It is undisputed that none of the references Petitioner identifies discloses the claimed compounds. Instead, Petitioner asserts that a skilled artisan would have made a multitude of changes to a prior art "lead compound," at specific positions—and, critically, no other changes—to arrive at the claimed compounds, which is essentially the same argument considered and rejected by the Examiner during prosecution. The Examiner did not materially err (or indeed err at all) in allowing the challenged claims, and Petitioner fails to identify Examiner error or facts that would justify reconsideration. Therefore, the Petition should be denied under section 325(d).

Third, the Petition is so weak on its face that discretionary denial is warranted. As explained below, the Petition does not come close to establishing a reasonable likelihood of unpatentability. First, Petitioner uses hindsight to select its alleged lead compound based only on structural similarity. Petitioner does not even attempt to show that a skilled artisan would have selected the lead compound over other prior art compounds, as Federal Circuit caselaw requires. Petitioner then applies hindsight on top of hindsight to pick and choose multiple specific modifications from prior art references that collectively disclose countless potential options, while failing to

sufficiently identify a motivation to make those particular changes or establishing a reasonable expectation of success in doing so.

Moreover, it is exceedingly rare for pharmaceutical compound claims to be invalidated as obvious, and even more so when the claims at issue recite a novel compound rather than, for example, an enantiomer or polymorph thereof. And for good reason. It is extraordinarily difficult to develop new and useful medicines; it takes years of risk, effort, and investment, and due to the unpredictability of pharmaceutical development, only a tiny fraction of candidate compounds succeed. What's more, the '780 patent does not protect just any drug, it protects tirzepatide, one of the most important pharmaceutical inventions in modern medicine.

Finally, Petitioner's inappropriate use of PTAB proceedings to gain leverage in a parallel litigation that does not involve the '780 patent further supports discretionary denial. Petitioner is a compounding pharmacy. It sells non-FDA approved copies of Lilly's groundbreaking tirzepatide drugs, unfairly profiting from Lilly's extensive investment in research, development, and innovation. In April of this year, Lilly sued Petitioner for engaging in deceptive practices and misleading advertising related to its unapproved compounded products. The '780 patent is not asserted in that litigation or in any other against Petitioner. And yet, despite having notice of the '780 patent for years and having done nothing to challenge Lilly's settled expectations, suddenly within one month of being sued by Lilly, Petitioner

brought this challenge to Lilly's tirzepatide compound patent in retaliation for Lilly's lawsuit. This is a misuse of the entire PTAB system, and a waste of the Director's and the PTAB's time and resources. Petitioner's motives are clear, and the Director need not and should not reward such conduct with institution.

For at least these four reasons, the Director should deny institution.¹

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 Since the filing of this Petition, a second IPR challenging the '780 Patent has been filed. *BPI Labs, LLC v. Eli Lilly & Co.*, IPR2025-001346, Paper 2 (P.T.A.B. Aug. 4, 2025). As Lilly will show at the appropriate time, discretionary denial of that second Petition is warranted for many of the same reasons set forth herein.

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 mono-agonists 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. Stimulation of glucagon and GLP-2 receptors (additional incretin receptors), should be minimized in order to maximize blood glucose lowering and reduce carcinogenic risks, respectively. *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 do not show the clinical safety or efficacy needed to overcome the limitations of prior art mono-agonists. *See generally* Ex. 1008 (WO 2013/164483, "Just"), Ex. 2001 (WO 2014/192284, "Asami"), and Ex. 1007 (WO 2011/119657, "Alsina-Fernandez"). Indeed, 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)).

Based on these limitations in the prior art, 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.*, 2:13-15. 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:

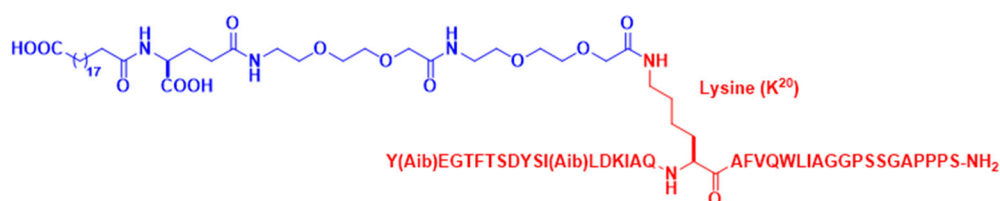
Accordingly, certain compounds of the present invention have lower potential for immunogenicity and injection site reactions than certain GIP-GLP-1 co-agonist compounds in the art. Certain compounds of the present invention have potential for producing weight loss in patients Furthermore, certain compounds 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. Accordingly, an

embodiment of the present invention provides a compound of Formula I:



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 $[(2-(2\text{-Amino-ethoxy})\text{-ethoxy})\text{-acetyl}]_2-(\gamma\text{Glu})_a\text{-CO}-(\text{CH}_2)_b\text{-CO}_2\text{H}$ 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., 2:41-65. Formula I in the '780 patent discloses 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.*, cl. 1. Tirzepatide is also recited in claim 15 of the '780 patent 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 a backbone of 39 amino acids (shown in red in the image above), as well as 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 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 tirzepatide molecule, including both the red and blue portions.

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

Alsina-Fernandez is discussed twice in the specification of the '780 patent and describes Lilly's early efforts to develop GIP/GLP-1 dual agonist compounds. Ex. 1004 (“'780 Patent FH”), 89, 114; *see also* '780 Patent, 1:55-57, 20:54-64. Alsina-Fernandez is entitled “Novel Peptides and Methods for Their Preparation and Use” and discloses a collection of GIP/GLP-1 dual agonists based on the native GIP sequence with optional substitution of backbone amino acids, as well as C-terminal modifications (e.g., addition of cysteine residues and PEGylation). Alsina-Fernandez, Title, 1:3-7, 2:12-26, 5:28-6:24, 9:6-11:19, cl. 1. Alsina-Fernandez discloses a genus of compounds taught in SEQ ID NO:1, stating:

The present invention provides a peptide comprising the sequence:

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

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wherein Xaa¹ at position 22 is Nal or Phe; Xaa² at position 43 is Cys or absent; Xaa³ at position 44 is Cys or absent; the C-terminal amino acid is optionally amidated; and provided that where Xaa² at position 43 or Xaa³ at position 44 is Cys, then either or both are optionally PEGylated.

Id., 2:12-25; *see also id.*, cl. 1.

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

Just is disclosed on the face of the '780 patent and was expressly considered by the Examiner during prosecution. Just, entitled "GIP-GLP-1 Dual Agonist Compounds and Methods," discloses billions of GIP/GLP-1 dual agonists with various structural modifications. *See, e.g.*, Just, Title, [0007]-[0020]. Just teaches many different options for each component of its disclosed compounds, including numerous different fatty acids, possible spacer moieties, and amino acid positions for acylation, and two or more amino acid choices at nearly every position on the amino acid backbone. *See id.*, [0056]-[0064], [0067], [0069].

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

Lau discloses the compound known as semaglutide, the active ingredient in Novo Nordisk's Ozempic®, Wegovy®, and Rybelsus® drug products. Ex.1010, 1:21-23. Semaglutide, Lau's Example 4, was referenced 28 times in the specification of the '780 patent. Lau, entitled "Acylated GLP-1 Compounds," discloses billions of GLP-1 *mono*-agonists when accounting for all of the many options across the various functional groups. Lau discloses numerous different fatty

acids and possible spacer moieties, and two or more amino acid choices at dozens of different positions on the amino acid backbone. Lau, 7:13-24:9. But 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 person could determine a structure-activity relationship (“SAR”) for the compounds. Equally important, there is no disclosure of any GIP/GLP-1 dual agonists in Lau; indeed, Petitioner admits that Lau’s disclosure of “semaglutide is ***not*** a dual agonist and is ***not the closest prior art.***” Pet. 79 (original emphasis)².

III. PROSECUTION HISTORY

The Examiner allowed the claims of the ’780 patent without any prior art rejections. *See generally* ’780 Patent FH. Importantly, 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

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

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, the core disclosure of Lau upon which Petitioner relies, 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, having dual agonist activity, have advantages over the mono-agonist 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, and found 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 other changes—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-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H) 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. THE DIRECTOR SHOULD NOT DISTURB LILLY'S STRONG SETTLED EXPECTATIONS

Lilly's long-settled expectations as to the '780 patent strongly favor discretionary denial. The '780 patent issued on October 25, 2016, almost *nine years* before Petitioner filed this IPR. That passage of time alone has routinely been held to justify discretionary denial. Indeed, the Director has repeatedly found that settled expectations warrant discretionary denial when less time had passed since a patent's

issuance. *See, e.g., Dabico Airport Sols., Inc. v. AXA Power APS*, IPR2025-00408, Paper 21 at 2-3 (P.T.A.B. June 18, 2025) (settled expectations in patent that “ha[d] been in force **almost eight years**” favored discretionary denial); *Yangtze Memory Techs. Co. v. Micron Tech., Inc.*, IPR2025-00498, -00499, -00500, -00501, Paper 11 at 2 (P.T.A.B. Aug. 14, 2025) (discretionarily denying based on “strong settled expectations” where challenged patents had been in force for **six years**); *HS Hyosung Advanced Materials Corp. v. Kolon Indus., Inc.*, IPR2025-00662, -00663, -00664, Paper 12 at 2-3 (P.T.A.B. Aug. 14, 2025) (discretionarily denying based on “strong settled expectations” for patents that had been in force for more than **six and seven years**); *Kahoot! AS v. Interstellar Inc.*, IPR2025-00696, Paper 12 at 2 (P.T.A.B. July 31, 2025) (discretionarily denying based on “strong settled expectations” where the challenged patent had “been in force for over **six years**”); *SmartSky Networks LLC v. Gogo Bus. Aviation LLC*, IPR2025-00672, Paper 10 at 2 (P.T.A.B. July 31, 2025) (discretionarily denying based on “strong settled expectations” where the challenged patent had “been in force for **seven years**”); *Amgen Inc. v. Bristol-Myers Squibb Co.*, IPR2025-00601, -00602, Paper 9 at 2-3 (P.T.A.B. July 24, 2025) (discretionarily denying based on “strong settled expectations” for patents that “ha[d] been in force for **seven and six years**”); *TankLogix, LLC v SitePro, Inc.*, IPR2025-00647, Paper 10 at 3 (P.T.A.B. July 31, 2025) (discretionarily denying based on “strong settled expectations” for a patent that had been in force for **seven**

years); *Cambridge Indus. USA, Inc. v. Applied Optoelectronics, Inc.*, IPR2025-00435, Paper 11 at 3 (P.T.A.B. June 26, 2025) (discretionarily denying based on strong settled expectations for a patent in force for *seven years*).

Lilly's settled expectations are particularly significant in this case for three reasons. **First**, Lilly has relied on the validity of the '780 patent in investing heavily in the research and development of tirzepatide for many years, and continuing today. **Second**, Lilly has applied the technology extensively in the relevant field, providing notice to the industry and widely publicizing its clinical trial results and obtaining FDA approval to commercialize tirzepatide as soon as possible. **Third**, there has been no relevant change in the law that would merit disrupting Lilly's strong settled expectations.

A. Lilly Relied On The '780 Patent In Heavily Investing In Tirzepatide

Lilly has invested an extraordinary amount in the development of tirzepatide. The Pharmaceutical Research and Manufacturers of America ("PhRMA"), a trade group representing biopharmaceutical research companies, estimates that, on average, it can cost \$2.6 billion to develop one new medicine. Ex. 2003, 1. Tirzepatide is no exception. Indeed, the large number of clinical trials Lilly has conducted in developing tirzepatide illustrates its massive investment.

In total, past or current Lilly tirzepatide clinical trials include 23 Phase I trials, 14 Phase II trials, 34 Phase III trials, 11 Phase IV trials, and one observational study,

summing to a grand total of 83 clinical trials. Exs. 2049, 2050. One publication estimated the average cost of clinical trials at \$4-5.26 million per Phase I trial, \$7-20 million per Phase II trial, and \$20-100+ million per Phase III trial. Ex. 2004, 3. Another publication notes that Phase III trials cost \$100 million *on average* and can cost up to \$500 million. Ex. 2005, 1-2. Phase IV trials range from \$100,000 for small targeted studies to tens of millions, with an average cost in the U.S. of \$5,856 per patient. Ex. 2006. Another publication found the median clinical trial cost in 2015 to 2016 to be \$19 million, with half of clinical trials falling between \$12 million and \$33 million. Ex. 2007, 1-2. At that time, the lowest clinical trial cost was \$2 million for a four-patient study, and the highest cost was \$347 million for a large Phase III study, of which Lilly has done many. *Id.* Lilly has plainly invested an enormous amount of time, money, and resources in the development of tirzepatide.

Further, Lilly is continuing to invest in tirzepatide today, investigating its safety and efficacy for treating many additional diseases and disorders, including heart failure with preserved ejection fraction, metabolic dysfunction-associated steatohepatitis, cardiovascular risk reduction, chronic kidney disease, plaque psoriasis, and psoriatic arthritis. Exs. 2049, 2050. Lilly's substantial and continuing investment in tirzepatide reflects its strong settled expectations.

B. Lilly Widely Publicized Its Tirzepatide Clinical Trials, Putting The Public On Notice Of Its Invention

Lilly has continually put the public on notice of its research and development of tirzepatide. Lilly initiated and publicly announced a Phase I clinical trial evaluating tirzepatide in 2016 and published the results of that trial in 2018. Ex. 2009; Ex. 2010. In July 2016, Lilly announced publicly that its new GIP/GLP-1 dual agonist “[a]chieved [a phase I] milestone” in diabetes treatment. Ex. 2011, 18 (Lilly Q2 2016 Earnings Presentation). Further, in October 2017, Lilly identified its new GIP/GLP-1 dual agonist (tirzepatide) in response to a question about what products investors should be “focused” on. Ex. 2012, 15-16 (Lilly Q3 2017 Earnings Call).

Soon thereafter, Lilly conducted and published the results of Phase II and III clinical trials, reporting impressive results and attracting substantial attention. *See, e.g.*, Ex. 2013 (Lilly Press Release (Oct. 4, 2018)) (discussing the promising results from a Phase 2b study); Ex. 2014; Ex. 2015, 2-3 (“results exceeded ... expectations”); Ex. 2016 (patented compound’s efficacy was “unprecedented”); Ex. 2017 (Lilly Press Release (Dec. 9, 2020)); Ex. 2018 (Lilly Press Release (Feb. 17, 2021)); Ex. 2019 (Lilly Press Release (June 25, 2021)); Ex. 2020 (Lilly Press Release (June 21, 2024)).

Lilly’s clinical study results were published in the most prestigious scientific journals, including the New England Journal of Medicine, the Lancet, and Nature.

See, e.g., Exs. 2021-2024; *see also* Ex. 2019 (Lilly Press Release (June 25, 2021)).

But they garnered attention far beyond the scientific community: the industry and countless news outlets took notice. *See, e.g.*, Ex. 2025, 2 (N.Y. Times (Apr. 28, 2022)) (the results are “very impressive”); Ex. 2026 (Medscape (June 4, 2022)) (tirzepatide achieved “‘unprecedented’ levels of weight loss in the vast majority of patients”).³ Investors likewise remarked on the incredible results, noting that they produced a significant rise in share price in response to top-line data from the Phase III clinical trial. Ex. 2041 (Nasdaq (Dec. 10, 2020)).

Following the positive clinical trial results, Lilly sought the FDA approval necessary to commercialize its invention. The FDA approved tirzepatide to treat type 2 diabetes in May 2022, chronic weight management in November 2023, and obstructive sleep apnea in December 2024. Ex. 2002 (Lilly Press Release (May 13,

³ *See also* Ex. 2027 (Diabetes Care (2023)); Ex. 2028 (Bus. Insider (June 6, 2022)); Ex. 2029 (Molecules (2022)); Ex. 2030 (Wall St. J. (Apr. 3, 2023)); Ex. 2031 (Drug Discovery & Dev. (Jun. 3, 2021)); Ex. 2032 (Drug Discovery & Dev. (Apr. 28, 2022)); Ex. 2033 (Nature Revs. Drug Discovery (May 20, 2022)); Ex. 2034 (Biopharma PEG (May 20, 2022)); Ex. 2035 (Drug Design, Dev. & Therapy (2022)); Ex. 2036 (diaTribe Learn (Sept. 21, 2022)); Ex. 2037 (Drs. Bus. Network (Apr. 28, 2025)); Ex. 2038 (Drug Discovery & Dev. (Oct. 16, 2023)).

2022)); Ex. 2042 (Lilly Press Release (Nov. 8, 2023)); Ex. 2043 (Lilly Press Release (Dec. 20, 2024)).

While “actual notice of a patent or of possible infringement is not necessary to create settled expectations,” Petitioner has known, or should have known, of the ’780 patent for many years. *See Dabico*, IPR2025-00408, Paper 21 at 3. As described above, Lilly widely publicized its clinical trials on tirzepatide beginning in 2016 and in numerous updates and publications thereafter. Any interested party could have easily determined, through a routine search, that tirzepatide was covered by the ’780 patent. Further, Lilly expressly put parties on notice of the ’780 patent upon FDA approval in 2022, listing the ’780 patent in the FDA’s Orange Book.⁴ Ex. 2044 (FDA, *Orange Book: Approved Drug Products* listing Tirzepatide and providing the date for listing the ’780 patent as June 9, 2022); *see Caraco Pharm. Labs., Ltd. v. Novo Nordisk A/S*, 566 U.S. 399, 420 (2012) (“[Orange Book listings] place both generic companies and the FDA on notice of their patents”); *see also Merck & Co., Inc. v. Hi-Tech Pharmacal Co.*, 482 F.3d 1317, 1319 (Fed. Cir. 2007) (“FDA publishes patent information on approved drug products in the ‘Orange Book,’ a register that provides notice of patents covering name brand drugs.”).

⁴ Mounjaro[®] has been on the market since May 2022 and Zepbound[®] since November 2023.

Petitioner's failure to seek earlier review favors discretionary denial.

C. There Is No Change In The Law That Would Merit Disrupting Lilly's Strong Settled Expectations

There has been no change in the law or new judicial precedent since the claims issued that would affect patentability. In particular, there has been no change in the law of structural obviousness or the "lead compound" test, which is the purported basis of Petitioner's challenge. And, as discussed below in Section VI.B., it is extremely rare for claims to novel pharmaceutical compounds to be invalidated for structural obviousness.

For the foregoing reasons, Lilly's settled expectations strongly favor discretionary denial.

V. THE DIRECTOR SHOULD DENY INSTITUTION UNDER SECTION 325(D)

Section 325(d) allows the Director to deny institution if the challenge to the patent is based on "substantially the same prior art or arguments previously" presented to the Office. 35 U.S.C. § 325(d); *see also* 37 C.F.R. § 42.4(a). Under section 325(d), the Board follows a two-part framework:

- (1) whether the same or substantially the same art previously was presented to the Office or whether the same or substantially the same arguments previously were presented to the Office; and

- (2) if either condition of [the] first part of the framework is satisfied, whether the petitioner has demonstrated that the Office erred in a manner material to the patentability of challenged claims.

Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential) (footnote omitted). The Board has further “clarifie[d] that a petitioner must provide an analysis” of how the Examiner erred and cannot “simply rely on its unpatentability contentions to imply that an error occurred.” *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 5 (P.T.A.B. May 19, 2025) (precedential). Thus, the Director may exercise discretion to deny institution if the petitioner fails to show that the Office erred in a manner material to patentability. *See, e.g., Advanced Bionics*, IPR2019-01469, Paper 6 at 8 (citing *Becton, Dickinson & Co. v. B. Braun Melsungen AG*, IPR2017-01586, Paper 8 at 24-25, 28 (P.T.A.B. Dec. 15, 2017) (precedential as to section III.C.5, first paragraph)). Notably, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* at 8-9.

In determining whether to exercise discretionary power under section 325(d), the Director considers the following non-exclusive factors, as articulated in *Becton*:

- (a) the similarities and material differences between the asserted art and the prior art involved during examination;

- (b) the cumulative nature of the asserted art and the prior art evaluated during examination;
- (c) the extent to which the asserted art was evaluated during examination, including whether the prior art was the basis for rejection;
- (d) the extent of the overlap between the arguments made during examination and the manner in which Petitioner relies on the prior art ...;
- (e) whether Petitioner has pointed out sufficiently how the Examiner erred in its evaluation of the asserted prior art; and
- (f) the extent to which additional evidence and facts presented in the Petition warrant reconsideration of the prior art or arguments.

See Becton, IPR2017-01586, Paper 8 at 17-18.

A. *Advanced Bionics* Step 1 (*Becton* Factors (a), (b), And (d)): Substantially The Same Art And Arguments Were Previously Presented To The Patent Office

The Petition raises one Ground: claims 1-7, 9-10, and 12-18 of the '780 patent are allegedly unpatentable as obvious over Alsina-Fernandez, Just, and Lau. Pet. 3, 22. Petitioner asserts that a skilled artisan would have selected the genus of compounds disclosed in Alsina-Fernandez SEQ ID NO:1 as a lead compound⁵ and

⁵ For simplicity of analysis, this brief refers to Alsina-Fernandez's SEQ ID NO:1 as Petitioner's "lead compound," but Petitioner's lead compound is a genus covering

then would have made numerous, specific modifications based on the disclosures in Just and Lau to arrive at the claimed compounds. For instance, Petitioner proposes deleting and adding specific amino acids in the backbone, adding a particular lipidated albumin-binding moiety, and adding a specific linker to connect it to the amino acid backbone, while making no other changes. Pet 23-24. As will be described further in the Patent Owner's Preliminary Response ("POPR") and below, Petitioner's arguments fail on the merits for several reasons. *See infra* Section VI.

But without even needing to consider the merits, the Director should deny institution because all three references in the Petition's Ground were considered by the Examiner or are cumulative of art before the Examiner during prosecution and Petitioner uses them to raise essentially the same obviousness argument properly rejected by the Examiner. This is precisely the type of petition Section 325(d) was enacted to address.

1. Just

Petitioner admits that, during prosecution of the '780 patent, the Examiner considered Just in addition to 12 other references. Pet. 7; '780 Patent FH, 36-40. Just was (1) cited in the application's specification ('780 Patent FH, 89; '780 Patent,

28 distinct compounds. Alsina-Fernandez, 2:12-25, cl. 1. Petitioner relies on the collective disclosure of this genus in its lead compound analysis.

1:55-57), (2) identified in an IDS ('780 Patent FH, 36-40), and (3) explicitly distinguished by the Examiner in the Reasons for Allowance (*id.*, 27-28). In the Reasons for Allowance, the Examiner stated that it would require “hindsight reasoning” to arrive at the claimed compounds from the disclosure of Just:

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

...

Therefore, in order to make the instantly claimed compounds one of ordinary skill in the art would have to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different from those preferred and reduced to practice in Just et al. Then, one of ordinary skill in the art would have to substitute at Gln at position 24 and a moiety of ([2-(2-Amino-ethoxy)-ethoxy]-acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H for the lipophilic substituent, ***but not make any***

other changes. To do so would require hindsight reasoning. Thus, the claimed compounds are both novel and unobvious over Just et al.

Id. Accordingly, there is no question that the Examiner considered Just and found the claims both novel and nonobvious over it. Thus, Just was before the Examiner and meets step 1 of the *Advanced Bionics* framework.

2. Alsina-Fernandez

a. Alsina-Fernandez Was Before The Examiner During Prosecution

Petitioner incorrectly asserts that Alsina-Fernandez was not before the Examiner during prosecution. Pet. 16. In fact, Alsina-Fernandez was cited ***twice*** in the specification that was before the Examiner. '780 Patent FH, 89, 114. An examiner reviews the specification and must consider the art cited therein in analyzing the patentability of the claims. The Manual of Patent Examining Procedure ("MPEP") instructs examiners to review the specification and all art cited therein. *See* MPEP § 707.05 ("The examiner ***must consider all the prior art references ... cited in the application*** or reexamination"); *id.* § 2103 ("***Examiners will review the complete specification***").

The Board has similarly held that references cited in the specification were before the examiner during prosecution. *See Apotex Inc. v. Celgene Corp.*, IPR2023-00512, Paper 7 at 50 (P.T.A.B. July 20, 2023) (holding a prior art reference was before the examiner because it was expressly cited in the specification of the

challenged patent); *Precision Planting LLC v. Maschio Gaspardo S.p.A.*, IPR2024-00008, Paper 12 at 21 (P.T.A.B. Mar. 26, 2024) (“[A]rguably, [applicant admitted prior art] was before the Examiner because it is part of the Specification.”).

Therefore, Alsina-Fernandez was before the Examiner during prosecution and meets step 1 of the *Advanced Bionics* framework.

b. Alsina-Fernandez Is Cumulative Of Art Before The Examiner During Prosecution

Besides being before the Examiner, Alsina-Fernandez meets step 1 of *Advanced Bionics* for an additional and independent reason: it is cumulative of art that was before the Examiner and Petitioner relies on it to make the same arguments the Examiner properly rejected during prosecution. The Board has repeatedly denied institution under section 325(d) when petitioners assert art cumulative of that before the examiner during prosecution. *See Vovomart (HK) Enters. Co. v. Office Kick, Inc.*, PGR2022-00048, Paper 14 at 12-13 (P.T.A.B. Jan. 12, 2023) (finding the art was cumulative of that before the examiner during prosecution); *Nespresso USA, Inc. v. K-Fee Sys. GmbH*, IPR2021-01222, Paper 9 at 13-14 (P.T.A.B. Jan. 18, 2022) (prior art was cumulative where it provided substantially similar disclosures of the same structural features and petitioner failed to explain how asserted art “differ[ed] in any material respect from” references before the examiner); *Fitesa Simpsonville, Inc. v. Procter & Gamble Co.*, IPR2023-01451, Paper 11 at 11-19 (P.T.A.B. Mar. 20, 2024) (prior art that disclosed substantially the same information as references

already considered by Office were “substantially the same art previously presented to the Office”).

Alsina-Fernandez is cumulative of Just, and Petitioner relies on Alsina-Fernandez to make essentially the same arguments that the Examiner properly rejected relative to Just. The Examiner cited Just as the closest prior art, but correctly allowed the claims of the '780 patent because they were novel and nonobvious over Just. '780 Patent FH, 27-28. The Examiner explained that to make the claimed compounds, one of ordinary skill would have to choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are different than those preferred and reduced to practice in Just. *Id.* Then, one of ordinary skill would have to substitute a Gln at position 24 and a particular moiety for the lipophilic substituent, but not make any other changes. *Id.* The Examiner properly explained that to do so would require hindsight reasoning. *Id.*

Like Just, Alsina-Fernandez discloses dual GIP/GLP-1 agonists that differ from the claims of the '780 patent in several important ways, such that only with hindsight could a skilled person arrive at the claimed compounds from Alsina-Fernandez. As will be detailed in the forthcoming POPR, Petitioner's obviousness theory requires several specific changes to the alleged lead compound (many of which encompass multiple decision points for each change), and ***no other changes***, none of which would have been obvious without improperly using the challenged

patent as a roadmap. The Examiner's correct conclusion that no skilled artisan would make such changes absent hindsight applies regardless of whether a skilled artisan starts with Just or Alsina-Fernandez. '780 Patent FH, 27-28. Accordingly, the Examiner previously considered substantially the same obviousness arguments presented by Petitioner and correctly found the claims novel and nonobvious over these arguments.

Moreover, Petitioner's own statements highlight the cumulative nature of the subject matter disclosed in Just and Alsina-Fernandez. For example, Petitioner asserts that Just teaches a genus of GIP/GLP-1 receptor dual agonists that "essentially encompasses" the N-terminal peptide sequence of Alsina-Fernandez. Pet. 23 ("[Just] teaches a genus of GIP/GLP-1 receptor dual agonists that essentially encompasses the N-terminal peptide sequence of [Alsina-Fernandez]."). Because the Examiner considered and rejected Just, which Petitioner concedes "essentially encompasses" the peptide sequence of Alsina-Fernandez, Just and Alsina-Fernandez are cumulative.

3. Lau

Petitioner relies on Lau for its disclosure of: (1) semaglutide and (2) the connection location on the amino acid backbone (Lys²⁰) for the fatty acid side chain, the linker, and the length of the fatty acid (C20). But (1) semaglutide was expressly

before the Examiner, and (2) Lau's other disclosure is cumulative of art before the Examiner.

First, Petitioner relies on Lau for its disclosure of semaglutide. Pet. 14-15, 19-20, 23-24, 40-41, 43-47, 75-77. But semaglutide and its structure were expressly before the Examiner during prosecution, as semaglutide is referenced 28 times and discussed at length in the '780 patent. *See, e.g.*, '780 Patent FH, 98 ("As used herein, 'semaglutide' refers to a chemically synthesized GLP-1 analogue that has the peptide backbone and overall compound structure of that found in CAS Registry Number 910463-68-2."); '780 Patent, 8:23-26 (same); *see also* '780 Patent FH, 89, 116-125; '780 Patent, 2:21-26, 22:18-28:16, Tables 7-9, 11-12, 14-15. This CAS Registry Number at the time of patenting (2015), included the peptide structure of semaglutide, as PubChem confirms the structure was added to the CAS Registry Number in 2012. Ex. 2045 (PubChem Substance Record, CAS Registry No. 910463-68-2) (listing the Deposit Date as March 21, 2012).

Second, Petitioner relies on both Just and Lau for disclosure of the connection location on the amino acid backbone (Lys²⁰) for the fatty acid side chain, the linker, and the length of the fatty acid. Pet. 40-47. Like Lau, as Petitioner itself argues, Just discloses conjugation of the linker and fatty acid at amino acid position 20. *Id.*, 40. Also like Lau, Just discloses many different options for linkers (called spacers in Just) and fatty acids. Just, [0063]-[0066], [0069] (disclosing dozens of possible

spacer moieties), [0056]-[0062] (disclosing numerous possible fatty acids, including a C20 fatty acid as found in tirzepatide). Accordingly, Lau is cumulative in relevant part to Just, and the portions of Lau Petitioner relies upon meet step 1 of *Advanced Bionics*.

Further, even if Lau's relevant disclosure had not been before the Examiner (it was), Lau adds little to the obviousness analysis. In fact, Just would have provided more guidance to a person of skill in the art than Lau because Just, unlike Lau, includes *in vitro* and *in vivo* test results for the disclosed compounds. Ultimately, Petitioner's reliance on the same primary references as those before the Examiner—Alsina-Fernandez and Just—as well as information disclosed in the specification (and now alleged to be in Lau), to make the same arguments rejected during prosecution, warrants discretionary denial. *See Dr. Reddy's Labs. S.A. v. Indivior UK Ltd.*, IPR2019-00328, Paper 21 at 17-18 (P.T.A.B. June 3, 2019) (denying institution under section 325(d), finding all but one reference was considered by the examiner and the secondary reference not considered by the examiner “suggests hindsight reconstruction and adds little, if anything, to the obviousness analysis,” and noting information provided in a separate secondary reference was also disclosed in the specification of the application leading to the challenged patent).

B. *Advanced Bionics* Step 2 (*Becton* Factors (c), (e), And (f)): Petitioner Has Failed To Identify Any Material Error

Petitioner has not met—and cannot meet—its burden to demonstrate that the Examiner materially erred in allowing the claims under the second prong of *Advanced Bionics*. Pet. 7-8; see *Ecto World*, IPR2024-01280, Paper 13 at 4-6 (holding petitioner must provide an analysis of how the examiner erred to avoid discretionary denial); see also, e.g., *Advanced Bionics*, IPR2019-01469, Paper 6 at 21 (“Petitioner must demonstrate that the Examiner erred in the evaluation of the prior art, for example, by showing that the Examiner misapprehended or overlooked specific teachings in the relevant prior art such that the error by the Office was material to the patentability of the challenged claims.”).

Petitioner’s conclusory, five-sentence argument alleging Examiner error does not demonstrate that the Examiner made any error—much less material error—in evaluating the prior art.⁶ See Pet. 7-8. Indeed, as will be explained further in the

⁶ Petitioner should not be allowed to attempt to cure its inadequate discussion of material Examiner error in forthcoming briefs. See, e.g., *Progenity, Inc. v. Natera, Inc.*, IPR2021-00266, Paper 8 at 5 (P.T.A.B. Apr. 1, 2021) (denying request for pre-institution reply on section 325(d) because Patent Owner’s arguments were “foreseeable” and “could have been comprehensively addressed by Petitioner in the Petition(s)"); *Merial, Inc. v. Intervet Int’l B.V.*, IPR2018-00919, Paper 11 at 2-3

POPR, the art establishes that the Examiner correctly found that arriving at the claimed compounds from the prior art would require hindsight.

1. Petitioner's Art And Arguments Were Considered During Examination (Factor (c))

The Examiner expressly and extensively evaluated Just, as demonstrated by the Notice of Allowance. Contrary to Petitioner's assertion, the Examiner's "primary basis" for distinguishing Just and allowing the '780 patent claims was not that Just "did not teach a preference for Gln (Q) at position 24." Pet. 7-8. Instead, she explained that making the claimed compounds would require several specific changes—and no others—to Just's compounds and that doing so would require hindsight. '780 Patent FH, 27-28. Petitioner fails to dispute or even address that finding.

The Examiner explained that Just did not disclose or render obvious Gln at position 24 and the claimed lipophilic substituent. *Id.* Further, she explained that to arrive at the claimed compounds, skilled artisans would have had to "choose options for positions 17, 27, 29, and 30-39, and for the site of lipophilic conjugation that are

(P.T.A.B. Aug. 21, 2018) (denying request for pre-institution reply because the "[325(d)] arguments Patent Owner raised in the Preliminary Response were reasonably foreseeable [and] Petitioner had an opportunity to address the issue in the Petition").

different from those preferred and reduced to practice in [Just].” *Id.*, 28. “Then, one of ordinary skill in the art would have to substitute a Gln at position 24 and a moiety of ([2-(2-Amino-ethoxy)-ethoxy]- acetyl)₂-(γGlu)₁₋₂-CO-(CH₂)₁₀₋₂₀-CO₂H for the lipophilic substituent, but not make any other changes.” *Id.* The Examiner found that “[t]o do so would require hindsight reasoning.” *Id.* Importantly, the Examiner explained that, even if Just had included Gln24 or the lipophilic substituent, “it would require hindsight reasoning to make the compounds claimed” because “all of the preferred embodiments and species” in Just’s broad genera “differ from the instant compounds at additional positions.” *Id.*

The Examiner’s reasoning applies with equal force to Alsina-Fernandez. Here, Petitioner’s lead compound (SEQ ID NO:1) is actually a genus of compounds, requiring a skilled artisan to choose from multiple options at positions 22 (Nal/F), 43-44 (optional cysteines), and at the C-terminus (optionally amidated). *See* Alsina-Fernandez, 2:12-31. Thus, as the Examiner explained for Just, a skilled artisan still “would have to choose options” for multiple positions within SEQ ID NO:1 of Alsina-Fernandez with no teaching or motivation to choose the claimed options. *See* ’780 Patent FH, 28. In addition, as the Examiner found with respect to Just, a skilled artisan would have had to add the precise lipophilic substituent with the precise linker (neither of which was disclosed by Alsina-Fernandez), at the right location (also not disclosed by Alsina-Fernandez). *See id.*, 27-28. And, while

Petitioner argues that the lipophilic substituent and linker are disclosed in Lau, as the Examiner properly found for Just, even with that disclosure “it would require hindsight reasoning” to make the claimed compounds. *Id.* As will be discussed in detail in the POPR, a skilled artisan would have had to make additional replacements and make one specific choice out of many, and no others, for numerous aspects throughout each compound to ultimately arrive at the claimed compounds.

Petitioner makes essentially the same obviousness argument that the Examiner considered and correctly rejected as requiring hindsight. To be sure, Petitioner here relies on a voluminous 169-page expert declaration as well to try to bolster its positions. But whether Petitioner had its expert opine for 169 or 1,690 pages, that does nothing to alter the fact that there is fundamentally nothing new for the Office to consider. The art in Petitioner's Ground was all considered—or is cumulative of art that was considered—and substantially the same arguments were already properly rejected during prosecution.

2. Petitioner Fails To Explain How The Examiner Erred (Factor (e))

Petitioner fails to show how the Examiner erred in allowing the claims of the '780 patent. In a recent precedential decision, the Board explained that “*a petitioner must provide an analysis* even when the asserted prior art is [of record], but the Examiner did not apply the reference.” *Ecto World*, IPR2024-01280, Paper 13 at 4-5. Moreover, “Petitioner bears the burden of showing that the Office erred.”

Nespresso, IPR2021-01222, Paper 9 at 29. Petitioner asserts that the Examiner “erroneously allowed the claims without rejection” (Pet. 8), but fails to meet its burden of proving material error. In fact, the Examiner did not err, materially or otherwise, in allowing the claims.

First, Petitioner incorrectly suggests that the Examiner erred by not identifying “prior art teachings establishing the effective [SAR] for dual GIP/GLP-1 receptor agonism.” *Id.* 7. Yet, Petitioner itself fails to identify any specific prior art teaching of a SAR relationship for dual GIP/GLP-1 receptor agonism in the prior art that the Examiner allegedly misapprehended or overlooked. Furthermore, and as will be explained in detail in the POPR, those of ordinary skill understood that SAR relationships are complex and unpredictable and that, as a result, SAR studies are iterative and experimentally onerous.

Second, Petitioner incorrectly asserts that the Examiner erred by not identifying “any teaching in the prior art that Gln (Q) was an appropriate amino acid residue at position 24” or of the “specific conjugated moiety recited in the claims” and using the absence of those teachings as “the primary basis for distinguishing [Just].” *Id.* 7-8. The Examiner correctly concluded that Just does not disclose the claimed amino acid at position 24 or the conjugated moiety. ’780 Patent FH, 27-28. But the Examiner also explained that “[e]ven if there were” such disclosure in Just, “it would require hindsight reasoning to make the compounds claimed in this

application because all of the preferred embodiments and species disclosed in [Just] differ from the instant compounds at additional positions.” *Id.* Petitioner fails to show how the Examiner materially erred in so finding.

Moreover, Petitioner fails to address, let alone establish any material error in, the Examiner's conclusion that modifications like those proposed in the Petition would require hindsight. The Examiner's reasoning is supported by a significant body of obviousness cases involving pharmaceutical compound patents. *See, e.g., Sanofi-Aventis U.S., LLC v. Dr. Reddy's Labs., Inc.*, 933 F.3d 1367, 1375-80 (Fed. Cir. 2019) (affirming district court's nonobviousness judgment “finding no motivation to make [two] substitutions on docetaxel to improve its activity against drug-resistant cancers,” and finding accused infringer's arguments were “emblematic of hindsight reasoning”); *Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (holding that “working backwards from [the claimed] compound, with the benefit of hindsight,” does not show the required motivation to make specific modifications to a lead compound).

3. Petitioner Presents No Other Evidence Or Facts Warranting Reconsideration (Factor (f))

Finally, Petitioner presents no additional evidence or facts in the Petition that would warrant reconsideration of the prior art or arguments. *See Nespresso*, IPR2021-01222, Paper 9 at 29-39 (the Board “look[s] for some explanation of how

or why ‘the extent to which additional evidence and facts presented in the petition warrant reconsideration of the prior art or arguments’”).

Petitioner’s reliance on Lau for its disclosure of semaglutide does not change the outcome or provide new evidence of unpatentability. Petitioner asserts that the Examiner “failed to identify any teaching in the prior art identifying the specific conjugated moiety recited in the claims,” as disclosed in Lau. Pet. 8. This is simply false. As explained above in Section V.A.3., semaglutide—which Petitioner asserts contains the specific conjugated moiety (Pet. 23-24)—is referenced in the ’780 specification **28 times**. Lau is thus definitively **not** “new” evidence, but is instead cumulative of prior art that was before the Examiner during prosecution.

Petitioner does not raise new art or arguments, and is instead asking for a do-over because it is dissatisfied with the Examiner’s conclusion. But the law is clear: “[a]t bottom, [the *Advanced Bionics*] framework reflects a commitment to defer to previous Office evaluations of the evidence of record unless material error is shown.” *Advanced Bionics*, IPR2019-01469, Paper 6 at 9. Further, “[i]f reasonable minds can disagree regarding the purported treatment of the art or arguments, it cannot be said that the Office erred in a manner material to patentability.” *Id.* The Director should discretionarily deny the Petition for this additional independent reason.

VI. THE MERITS OF THE PETITION ARE WEAK

The Petition is weak on the merits, as Lilly will establish more fully in its POPR. *See Interim Director Discretionary Process*, § II.C.i., USPTO, <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process> (last visited Aug. 18, 2025) (“[W]hen filing a brief for discretionary denial, a patent owner may direct attention to an anticipated POPR and evidence for a discussion of the merits.”).

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) (explaining, “[t]he Federal Circuit provides a two-prong analysis to determine whether a new chemical compound is *prima facie* obvious over particular prior art,” consisting of lead compound selection and prior art examination to assess whether there is a “reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success”); *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).

Petitioner has utterly failed to meet the legal requirements of the lead compound test in challenging the '780 patent. First, Petitioner fails to explain why a skilled artisan would have selected its proposed lead compound over other prior art compounds, instead selecting its lead compound based entirely on hindsight. Next, Petitioner improperly uses hindsight to make multiple specific modifications—but not others—to arrive at the claimed compounds. Finally, Petitioner fails to establish a reasonable expectation of success. Petitioner's analysis is legally deficient and 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*, 913 F.3d at 1089. The Director should discretionarily deny the Petition for this additional reason.

A. Petitioner's Lead Compound Analysis Is Legally Deficient

Petitioner fails to satisfy the first prong of the lead compound test: to show 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 Labs., 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.*

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 “over other compounds in the prior art.” *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, 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 Lys²⁰-conjugation to a promising albumin-binding moiety.

Pet. 26.

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.

Id. 76-77. Likewise, Petitioner's expert offers nothing better, effectively parroting the Petition (despite submitting a 169-page declaration). *See* Ex. 1002 (Cornish Decl.), ¶¶ 139, 144. Neither Petitioner nor its expert provides any discussion or analysis of any other potential lead compounds or 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. *Otsuka*, 678 F.3d at 1292, 1296 (affirming the district court's "careful analysis [that] exposed the Defendant's 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." *Daichi*, 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 even mentioned by Petitioner are GIP/GLP-1 dual agonism and half-life. Pet. 26, 77. But Petitioner's asserted prior art references (i.e., 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 (Ex. 1061), 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. The Board has found

human clinical studies “particularly relevant” to lead compound selection in prior cases. *See, e.g., Mylan Pharms.*, IPR2023-00722, Paper 9 at 28 (“We find particularly relevant the status of clinical investigations for GLP-1 analogs as of the filing date of the ’122 patent.”). But Petitioner in this case provides no explanation whatsoever of why a skilled person would have selected Alsina-Fernandez’s SEQ ID NO:1 over any of the other GIP/GLP-1 dual agonists in the prior art.

Notably, Petitioner asserts that a fatty acid side chain and exenatide C-terminal motif confer obvious benefits as compared to the C-terminal tail in its selected lead compound. Pet. 26-28, 45-46. But many of the GIP/GLP-1 dual agonists taught by the prior art include a fatty acid side chain and an exenatide C-terminal motif. *See, e.g., Just*, Table 2. Thus, by Petitioner’s own logic, a skilled artisan would have been motivated to choose one of those GIP/GLP-1 agonists as a lead compound instead of Alsina-Fernandez’s SEQ ID NO:1.

“While the lead compound analysis must, in keeping with *KSR*, not rigidly focus on the selection of a single, best lead compound ..., the analysis still requires the challenger to demonstrate ... that one of ordinary skill in the art would have had a reason to select a proposed lead compound or compounds *over other compounds in the prior art.*” *Daiichi*, 619 F.3d at 1354. Because Petitioner has not even attempted to explain why a POSA would have selected Alsina-Fernandez’s

SEQ ID NO:1 over other prior art compounds, Petitioner's lead compound analysis is legally deficient as a matter of law.

This flaw is fatal and Petitioner cannot rely on subsequent briefing to remedy it. *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 sole obviousness ground, the Petition fails on the merits.

Moreover, and as will be explained in the POPR (incorporated by reference herein), the Petition also fails on the merits because it does not sufficiently identify a motivation for each of the required changes to its proposed lead compound (even if it were properly identified). Further, the Petition fails to establish a reasonable expectation of success in making the many modifications it proposes (and no others).

B. It Is Extraordinarily Rare For Pharmaceutical Compound Patents To Be Found Obvious, For Good Reason.

Petitioner's failure to show that the challenged claims would have been obvious is not surprising: pharmaceutical compound patents, like Lilly's '780 patent, are rarely held invalid for obviousness. This is due, in large part, to the unpredictability of drug discovery and development. *See Otsuka*, 678 F.3d at 1291-

93, 1298 (explaining “[a]s *KSR* makes clear, predictability is a vital consideration in the obviousness analysis,” and rejecting a lead compound obviousness argument where drug discovery was “very unpredictable”).

As courts have recognized for years, it is exceedingly difficult to create a novel compound that is safe and effective in humans for treating an illness or disease. This is illustrated by the thousands of compounds that have failed in drug development, despite significant resources invested in and innovative minds working for their success. Ex. 2046, 3050-51, 3059 (*Acta Pharmaceutica Sinica B* (2022)); Ex. 2047, 15 (*Biotechnology Innovation Org. (BIO)* (Feb. 2021)) (estimating success rate of biologics at 9%); Ex. 2048, 496 (*Nature Revs. Drug Discovery* (2019)) (disclosing Figure 2 showing low probability of progressing from Phase I to launch across many therapeutic areas). As such, when a new compound is invented that safely and effectively treats a disease better than any medication or other treatment method before it, the patent for that innovation is typically extremely strong.

In this case, Petitioner asks the Board to invalidate the '780 patent without identifying a single analogous case applying a lead compound analysis. Even the one structural obviousness case cited by Petitioner—*In re Dillon*—is inapposite because it concerned an obviousness rejection during prosecution and was not decided based on the lead compound test. 919 F.2d 688, 690 (Fed. Cir. 1990) (en

banc). There, the Federal Circuit affirmed the Board's rejection of pending claims related to the inclusion of tetra-orthoester compounds in hydrocarbon fuel compositions. *Id.* Far from claiming a novel compound, as in this case, the claimed "tetra-orthoesters [were] a known class of chemical compounds," and only their combination with hydrocarbon fuel was not disclosed in the prior art. *Id.* at 691. But the tetra-orthoester "additives in the new compositions [were] structurally similar to [tri-orthoester] additives in known compositions." *Id.*; see also *Sawai*, IPR2018-00079, Paper 7 at 14 ("Critically, *Dillon* relates to the rejection-and-response regime of patent examination, rather than the adjudicatory process of an *inter partes* review."). *Dillon*, therefore, does not support Petitioner's obviousness theory.

Lilly's research yielded only three cases finding a novel pharmaceutical compound claim obvious based on a "lead compound" analysis. See *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967 (Fed. Cir. 2014); *Alzheon Inc. v. Risen (Suzhou) Pharma Tech Co.*, IPR2021-00347, Paper 53 (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 (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). Each is easily distinguishable

from the facts here and, if anything, underscores that the claims challenged here are *nonobvious*.

First, in *Bristol-Myers*, the court evaluated obviousness of entecavir, which had just one modification from the prior art lead compound 2'-CDG. *See* 752 F.3d at 969-70. In addition, unique evidentiary circumstances supported a finding of obviousness. For instance, patent owner's expert *conceded* that: (1) the proposed lead compound was a "promising compound" (*id.* at 974); (2) there were limited conservative known substitutions that could have been made at the single position of the lead compound that differed from the claimed compound (*id.* at 974-75); and (3) skilled artisans would have had reason to make similar substitutions based on the prior art (*id.* at 975).

Similarly, in both Board cases finding unpatentability under the lead compound test, the claimed compound differed from the prior art by only a single isotopic substitution (deuteration), and isotopic substitution of the lead compounds was taught in the prior art (just not necessarily at the same position *and* of the same type as the claimed invention). *See Alzheon*, IPR2021-00347, Paper 53 at 54; *id.* at 5; *id.* at 66; *Incyte*, IPR2017-01256, Paper 119 at 23-24; *id.* at 5-6, 13-14; *see also Sun*, 2023 WL 5370639 at *1-2, 5.

This case is nothing like those three. Here, Petitioner provides no analysis supporting its selection of a lead compound over others in the prior art. Further,

numerous substantial modifications would have been required to arrive at the claimed compounds from Petitioner's alleged lead compound. The only way to (1) select Petitioner's lead compound, and (2) make each of the required changes but no others is with hindsight. 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 Alsina-Fernandez's SEQ ID NO:1 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 will be explained in the POPR, Petitioner similarly fails to establish a motivation to modify the lead compound to arrive at the claimed compounds and a reasonable expectation of success in doing so. But worse, Petitioner fails to establish that a skilled artisan would have selected its lead compound over other prior art compounds in the first place. *Supra* Section VI.A. Petitioner does not come close to showing a reasonable likelihood that the claimed compounds would have been obvious over the prior art, and this additional reason supports discretionary denial.

VII. THE DIRECTOR SHOULD REJECT PETITIONER'S LITIGATION TACTICS

This Petition should be discretionarily denied for one additional reason: Petitioner filed it in a transparent attempt to gain leverage in a parallel litigation in which the '780 patent is not even asserted. This explains why Petitioner challenged the '780 patent now rather than earlier, relied on cumulative art and arguments, and submitted a weak petition on the merits. Petitioner's tactics not only compromise the efficiency and integrity of the IPR process, but are an abuse of the Board's time and resources.

The month before the Petition was filed, in April 2025, Lilly sued Petitioner in district court, asserting that Petitioner engaged in false and deceptive advertising

of its compounded tirzepatide products in violation of state and federal law and in a way that put consumers at risk. *See Eli Lilly & Co. v. Empower Clinic Servs., LLC*, No. 2:25-cv-02183 (D.N.J. Apr. 1, 2025), Dkt. No. 1.⁷

The timing of the Petition—which comes nearly a decade into the patent's lifespan, after Petitioner knew or should have known of the '780 patent for years, and despite the '780 patent not being raised in the parallel litigation—demonstrates that the Petition's primary purpose is not to resolve issues of validity. Rather, the Petition is part of a strategic effort to gain leverage in the ongoing district court litigation and an inappropriate use of the Board's resources.

The circumstances here closely parallel those that the Director recently found favor discretionary denial. *See Sig Sauer Inc. v. Lone Star Future Weapons, Inc.*, IPR2025-00410, Paper 13 at 2 (P.T.A.B. June 26, 2025). In *Sig Sauer*, the challenged patent had issued over 10 years ago. *Id.* Further, the petitioner had subsequently developed a competing product without challenging the subject patent (*id.*); similarly here, Petitioner has for multiple years profited from Lilly's investment by selling a compounded version of tirzepatide without challenging the

⁷ This case has since been voluntarily dismissed and refiled in the Southern District of Texas. *Eli Lilly & Co. v. Empower Clinic Servs., LLC*, No. 4:25-cv-03464 (S.D. Tex. July 25, 2025), D.I. 1.

'780 patent. Additionally, in *Sig Sauer*, the petitioner filed its petition after the patent owner had filed a suit in district court which did not involve the challenged patent (*id.*); here, Lilly's district court suit against Petitioner, filed just one month before the Petition, does not involve the '780 patent. Based on these circumstances, including the settled expectations stemming from the 10-plus-year-old patent, the Director found in *Sig Sauer* that, where an IPR petition challenges a patent shortly after a litigation is filed between the same parties not involving the challenged patent, "there is a persuasive argument that the filing of the Petition may be inappropriate." *Id.* Just like in *Sig Sauer*, filing the present Petition was inappropriate and the Board should not reward such litigation tactics.

VIII. CONCLUSION

For the foregoing reasons, Lilly respectfully requests that the Director decline to institute *inter partes* review of the '780 patent.

Respectfully submitted,

Dated: August 20, 2025

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

I hereby certify that this Patent Owner's Brief on Discretionary Denial complies with the word count limitation outlined in the Memorandum on Interim Processes for PTAB Workload Management (P.T.A.B. Mar. 26, 2025) and consistent with 37 C.F.R. § 42.24 because the Patent Owner's Brief on Discretionary Denial contains a total of 11,440 words, which is the sum of 11,434 words calculated by Microsoft Word's word-count feature and 6 words hand-counted in the figures. This total excludes the cover page, signature block, and the parts of the Patent Owner's Brief on Discretionary Denial exempted by 37 C.F.R. § 42.24(a)(1).

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 20th day of August, 2025, a true and correct copy of the foregoing **Patent Owner's Brief on Discretionary Denial and all Exhibits** were served by electronic mail on Petitioner's lead and backup counsel at the following email addresses:

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