

Filed on behalf of: Eli Lilly & Co.

Entered: October 14, 2025

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BPI LABS, LLC,
Petitioner,

v.

ELI LILLY AND COMPANY,
Patent Owner.

Case IPR2025-01346
Patent 9,474,780

PATENT OWNER'S BRIEF ON DISCRETIONARY DENIAL

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I. INTRODUCTION

Patent Owner Eli Lilly & Co. (“Lilly”) respectfully requests that the Director deny the Petition filed by BPI Labs, LLC (“Petitioner” or “BPI”) challenging U.S. Patent No. 9,474,780 (the “’780 patent”). BPI’s Petition retreads a prior IPR Petition filed by Empower, which the Deputy Director recently denied in view of Lilly’s strong settled expectations in the ’780 patent. *Empower Clinic Servs., L.L.C. (d/b/a Empower Pharmacy) 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). Just as in *Empower*, the Deputy Director should deny institution here, for at least four reasons.

First, as in *Empower*, Lilly’s “strong settled expectations” favor discretionary denial. The ’780 patent issued almost nine years ago, and Lilly relied on the patent’s validity when deciding to invest billions of dollars in the development, commercialization, and manufacturing of tirzepatide, the active ingredient of Lilly’s revolutionary drug products that treat millions of Americans suffering from diabetes, obesity, and sleep apnea: Mounjaro® and Zepbound®. Further, Lilly widely reported its tirzepatide studies and publicly listed the ’780 patent in the FDA’s Orange Book. Petitioner has known, or should have known, of the ’780 patent for many years and

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, denial is warranted under 35 U.S.C. § 325(d) because, like Empower, BPI relies on the same or cumulative art to raise substantially the same arguments addressed by the Examiner during prosecution. The Petition's sole Ground relies on Alsina-Fernandez, DiMarchi, and Lau. All three are old news. For instance, Lilly cited Alsina-Fernandez twice in the '780 patent's specification, including in the very first column, and the Examiner-requested Search Results identified Alsina-Fernandez and its SEQ ID NOs: 1–5 in its first four pages. In addition, DiMarchi is materially identical in all relevant respects to another DiMarchi reference (“DiMarchi '807”) that was considered during prosecution and appears on the face of the '780 patent. Further, Lilly referenced Lau's core subject matter (semaglutide) 28 times in the specification, and the Search Results referred to semaglutide 12 times. And whereas Empower alleged examiner error in its Petition and briefing (which the Deputy Director found “not persuasive”), BPI *does not even mention* examiner error or otherwise address the '780 patent's prosecution history.

Third, the Petition is exceptionally weak on the merits—it does not come close to establishing a reasonable likelihood of unpatentability. Like Empower, BPI uses hindsight to select its lead compound, ignoring countless other prior art compounds and cherry-picking data that support its arguments while ignoring other data that do

not. BPI then applies hindsight on top of hindsight to select multiple specific modifications from references that collectively disclose countless potential options, while failing to sufficiently identify a motivation to make those particular changes (and no others) or establishing a reasonable expectation of success in doing so. Moreover, it is extremely rare for pharmaceutical compound claims to be invalidated as obvious, and BPI has not identified a single case that would support finding the challenged claims obvious here.

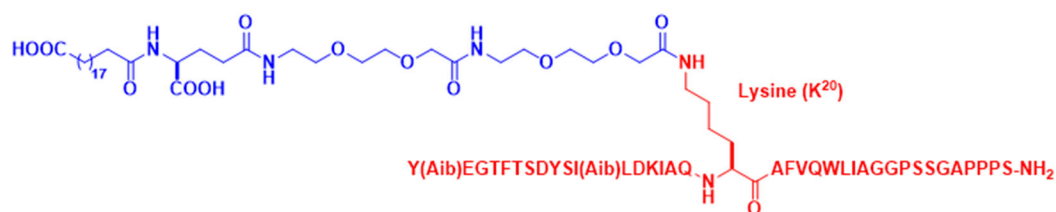
Finally, the Petition should be denied as redundant to Empower's materially identical Petition. Over two months before this Petition was filed, Empower challenged all the claims of the '780 patent that BPI now challenges, based on two of the same references asserted here. *Empower*, IPR2025-01024, Paper 2. BPI uses Empower's Petition as a blueprint, merely substituting one secondary reference for another and forcing Lilly to expend additional resources defending its patent in a concurrent proceeding. BPI's Petition is as weak as Empower's and the Deputy Director's reasons for denying Empower's Petition apply equally here. Instituting review would be inefficient and a waste of the Board's limited resources.

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

A. The '780 Patent (Ex. 1001). The '780 patent 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 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 gastrointestinal effects, which hindered full efficacy for glycemic control and weight loss. *Id.*, 1:36-39. These molecules also had issues such as rapid degradation, short-term metabolic control, immunogenicity, injection site reactions, and stimulation of glucagon and GLP-2 receptors (additional incretin receptors). *Id.*, 1:39-54, 1:65-2:3. Based on these prior art limitations, there was a need for a "balanced co-agonist" that targeted GIP and GLP-1 receptors, provided improved glycemic control and adequate stability, had a low immunogenicity potential, and supported once-weekly dosing. *Id.*, 2:27-29; *see id.*, 2:12-15, 2:33-40, 5:45-49. The '780 patent discloses and claims Formula I compounds, including tirzepatide, that met those needs. *Id.*, 2:41-65. Tirzepatide is specifically recited in claim 15 and has the following structure:



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

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

describes Lilly's early efforts to develop GIP/GLP-1 dual agonists. Its compounds are based on native GIP with optional substitution of backbone amino acids, as well as C-terminal modifications (e.g., addition of cysteine residues and PEGylation).

C. WO 2010/011439 A2 (DiMarchi) (Ex. 1017). DiMarchi describes *glucagon* analogs that exhibit GIP, GLP-1, and/or glucagon activity. It discloses billions of mono, dual, and tri-agonists that include many different fatty acids, spacer moieties, and amino acid choices along many positions of the amino acid backbone.

D. WO 2006/097537 A2 (Lau) (Ex. 1009). Lau discloses billions of GLP-1 *mono*agonists, including semaglutide. Lau's GLP-1 agonists include many different fatty acid and spacer moieties, and two or more amino acid choices at dozens of different positions on the amino acid backbone.

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 amino acid sequence of Petitioner's alleged lead compound (identified as SEQ ID NO: 5) were referenced in the Examiner's Search Results (Ex. 2088), which Petitioner's file history "Excerpts" (Ex. 1004) omitted. *Second*, the Examiner reviewed DiMarchi '807 (WO

2010/071807 A1, Ex. 2089), which contains materially identical disclosures as 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, WO 2013/164483 A1 ("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-Amino-ethoxy)-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**."¹ *Id.*, 27-28.

¹ Emphases added and citations omitted throughout unless otherwise noted.

IV. STRONG SETTLED EXPECTATIONS WARRANT DENIAL

As the Deputy Director has already found, Lilly's "strong settled expectations" favor discretionary denial. *See Empower*, IPR2025-01024, Paper 15 at 2. The '780 patent issued on October 25, 2016, almost **nine years** before Petitioner filed this IPR. *Id.* The Director has repeatedly found that settled expectations warrant discretionary denial when **less time** passed since issuance. *E.g., Dabico Airport Sols., Inc. v. AXA Power APS*, IPR2025-00408, Paper 21 at 2-3 (P.T.A.B. June 18, 2025) (patent "in force [for] almost eight years"); *Yangtze Memory Techs. Co. v. Micron Tech., Inc.*, IPR2025-00498, -00499, -00500, -00501, Paper 11 at 2 (P.T.A.B. Aug. 14, 2025) (patents in force for six years).

Lilly's settled expectations are particularly strong here, for three reasons. *First*, as the Deputy Director found, Lilly "has made, and continues to make, substantial investments of time, money, and resources" developing and commercializing tirzepatide. *See Empower*, IPR2025-01024, Paper 15 at 2. The Pharmaceutical Research and Manufacturers of America estimates an average cost of \$2.6 billion to develop a new medicine. Ex. 2003, 1. Tirzepatide is no exception. Lilly has conducted **over 80** tirzepatide clinical trials, all aimed at showing that its patented invention is safe and/or effective. Exs. 2049-2050. These studies take years to complete and range in cost from hundreds of thousands of dollars on the low end to over one hundred million dollars on the high end. *E.g.*, Ex. 2004, 3;

Ex. 2005, 1-2; Ex. 2006. In 2024, Lilly also launched Zepbound® in single-dose vials to expand access and affordability. Ex. 2090. And Lilly has committed \$50 billion in infrastructure investments for drug research and manufacture in the U.S., creating thousands of U.S. jobs, in no small part relying on the '780 patent and its protection of Lilly's blockbuster tirzepatide products. Ex. 2091 (announcing \$50 billion investment in U.S. manufacturing since 2020); Ex. 2092 (announcing \$9 billion investment in new Indiana tirzepatide manufacturing site).

Second, Petitioner has known, or should have known, of the '780 patent for many years. *See Dabico*, IPR2025-00408, Paper 21 at 3. As the Deputy Director noted, Lilly "listed the ['780] patent in the FDA's Orange Book in 2022," expressly putting parties on notice of the patent. *Empower*, IPR2025-01024, Paper 15 at 2; Ex. 2044; *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"). Petitioner's real party-in-interest, Belcher Pharmaceuticals, LLC, is a generic drug company on notice of Lilly's patents by the Orange Book listings. Pet. 4; Ex. 2094 (Belcher Website).

Lilly also widely publicized its research and manufacturing investments, announcing its tirzepatide progress beginning as early as 2016, and continuing to notify the public of its advancements as tirzepatide progressed through clinical trials. *E.g.*, Ex. 2009, 1 (announcing Phase I trial in 2016); Ex. 2010, 1 (publishing Phase

I results in 2018); Ex. 2011, 18 (announcing GIP/GLP-1 agonist progress); Ex. 2013 (discussing Phase 2b study results); Ex. 2015, 2-3 (“results exceeded ... expectations”); Ex. 2016 (patented compound’s efficacy was “unprecedented”); Exs. 2017-2020 (similar). Lilly’s results were published in prestigious scientific journals, *e.g.*, Exs. 2014, 2021-2024, garnered media attention far beyond the scientific community, *e.g.*, Exs. 2025-2038, and led to a significant rise in Lilly’s share price, *e.g.*, Ex. 2041.

Third, there has been no change in the law since the claims issued that would affect patentability. Indeed, the law is squarely against Petitioner—it is extremely rare for claims to novel pharmaceutical compounds to be invalidated for obviousness under any circumstances, much less these. *See* Section VI.B, *infra*.

V. SECTION 325(D) WARRANTS DENIAL

Institution denial is warranted because BPI’s challenge, like Empower’s, is based on “substantially the same prior art or arguments” previously presented to the Office. *See* 35 U.S.C. § 325(d); *see also* 37 C.F.R. § 42.4(a). Under § 325(d), the Board follows the *Advanced Bionics* two-part test, first assessing whether the art and arguments are substantially the same as those already presented to the Office and, if so, determining if the Office erred in a manner material to patentability. *See Advanced Bionics, LLC v. MED-EL Elektromedizinische Geräte GmbH*, IPR2019-01469, Paper 6 at 8 (P.T.A.B. Feb. 13, 2020) (precedential); *see also Becton*,

Dickinson & Co. v. B. Braun Melsungen AG, IPR2017-01586, Paper 8 at 17-18 (P.T.A.B. Dec. 15, 2017) (precedential as to section III.C.5, first paragraph) (setting forth non-exclusive factors (a)-(f) to consider in § 325(d) analysis).

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

The Petition's sole Ground asserts that the challenged claims are obvious over Alsina-Fernandez in view of DiMarchi and Lau. Pet. 7. Petitioner contends that a skilled artisan would have selected Alsina-Fernandez Example 2 (SEQ ID NO:5) as a lead compound and then made numerous, specific modifications based on DiMarchi's and Lau's disclosures to arrive at the claimed compounds. As explained below and as will be described in greater detail in the Patent Owner's Preliminary Response ("POPR"), Petitioner's arguments fail on the merits for several reasons. *See* Section VI, *infra*.

But before even reaching the merits, the Director should deny institution because all three references in Petitioner's Ground were considered by or are cumulative of the art before the Examiner. Petitioner uses this duplicative art to raise essentially the same obviousness argument properly rejected by the Examiner.

First, Lilly raised Alsina-Fernandez and its significance twice in the specification. '780 Patent FH, 89, 114 (identifying Alsina-Fernandez as disclosing compounds exhibiting GIP and GLP-1 activity); *see* Pet. 2 (conceding patent "cites to Alsina-Fernandez"); *id.* at 8, 74, 76 (similar). Because an examiner must review

the specification and the art cited therein when assessing patentability, references cited in the specification are before the examiner. *See* MPEP § 707.05 (“[E]xaminer[s] must consider all the prior art references ... cited in the application”); *id.* § 2103 (“Examiners will review the complete specification”); *Apotex Inc. v. Celgene Corp.*, IPR2023-00512, Paper 7 at 50 (P.T.A.B. July 20, 2023) (reference was before examiner because it was “expressly cited in the [patent’s] [s]pecification”). “[P]rior art described in the specification[] is expected to be considered by the Examiner.” *Polaroid Corp. v. Eastman Kodak Co.*, 641 F. Supp. 828, 833 (D. Mass. 1985), *aff’d*, 789 F.2d 1556 (Fed. Cir. 1986); *see Ind. Mills & Mfg., Inc. v. Dorel Indus. Inc.*, 458 F. Supp. 2d 890, 931 (S.D. Ind. 2006) (court “presumes that the examiner considered [the references] because those references were clearly cited in the specification”). In addition, the Search Results identified Alsina-Fernandez and its SEQ ID Nos: 1–5 in its first four pages. Ex. 2088, 1-4. Alsina-Fernandez was thus before the Examiner and meets *Advanced Bionics* step 1.

Alsina-Fernandez also meets *Advanced Bionics* step 1 for an independent reason: Alsina-Fernandez is cumulative of Just, which the Examiner found to be the closest prior art, and Petitioner relies on it to make essentially the same arguments the Examiner properly rejected as to Just. ’780 Patent FH, 27. To arrive at the claimed compounds, both Just’s and Alsina-Fernandez’s GIP/GLP-1 dual agonists would require multiple modifications that a skilled artisan would pursue only with

the benefit of hindsight. As the POPR will detail, Petitioner's obviousness theory requires several specific changes to the alleged lead compound—and *no others*—encompassing multiple decision points for each change. These changes would not have been obvious without using the '780 patent as a roadmap. The Examiner's conclusion that no skilled artisan would make such changes absent hindsight applies equally to Alsina-Fernandez as it did to Just. '780 Patent FH, 27-28.

Second, DiMarchi is cumulative of DiMarchi '807, which was considered during prosecution and appears on the face of the '780 patent. All of the DiMarchi teachings Petitioner points to are materially identical to those in DiMarchi '807. For instance, according to Petitioner, "DiMarchi discloses that increased activity at the GLP-1 receptor is provided by adding a C-terminal extension peptide such as GPSSGAPPPS or XGPSSGAPPPS to the C-terminus (i.e., the exendin C-terminal tail)." Pet. 25-26 (citing Ex. 1017, 5:7-11). But DiMarchi '807 includes a statement that is *substantively identical* to the one Petitioner cites. *See* DiMarchi '807, 110:1-4. Likewise, according to Petitioner, "DiMarchi discloses that glucagon peptides having a glycine substitution for threonine at position 29 and the C-terminal extension of GPSSGAPPPS is *four times* as potent at the GLP-1 receptor as native glucagon modified to include the C-terminal extension." Pet. 26 (emphasis original) (citing Ex. 1017, 55:10-15). But DiMarchi '807 includes the *exact same statement* (other than renumbering the SEQ ID). *See* DiMarchi '807, 113:23-28. Petitioner

also cites DiMarchi for secondary points that DiMarchi '807 likewise discloses:

Petition	DiMarchi '807		Petition	DiMarchi '807
Terminal amide. Pet. 46-47.	139:18-19		Preferred acylation locations. Pet. 56-57.	49:28-51:6
Preferred design strategy. Pet. 46.	218 at Table 15		Spacer attached to Lys. Pet. 57.	50:14-53:18
Peptide injection. Pet. 48.	236:14-16		C8-C20 fatty acid. Pet. 60.	58:11-17
Lys ²⁰ substitution. Pet. 55-56.	109:8-17		Acylation prolongs half-life. Pet. 26.	112:15-27
Spacer acylation. Pet. 56-57.	50:2-24		Formulation/treatment. Pet. 69-70.	2:10-31; 235:8-27

In short, *every* DiMarchi disclosure cited by Petitioner is substantively in DiMarchi '807 as well.

Third, Petitioner relies on disclosures from Lau that were either before—or are cumulative of the art that was before—the Examiner. Petitioner cites Lau for semaglutide and the connection location on the amino acid backbone (Lys²⁰) for the fatty acid side chain, the linker, and the length of the fatty acid (C16, C18, C20). Pet. 22-24, 50-62. But semaglutide and its structure were considered, with semaglutide referenced **28 times** in the '780 patent and **12 times** in the Search Results, and the claimed albumin binding moieties appear **more than two dozen times** in the Search Results. *Supra* Section III. Moreover, Lau's conjugation disclosure is cumulative of Just's, which the Examiner considered. *Id.* Like Lau, Just discloses conjugation of the linker and fatty acid at position 20 and many options for linkers ("spacers" in Just) and fatty acids. Just, [0067]; *id.*, [0063]-[0066], [0069] (disclosing spacers),

[0056]-[0062] (disclosing fatty acids, e.g., C20 fatty acid as in tirzepatide).

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

Petitioner likewise has not met—and cannot meet—its burden to show that the Examiner materially erred in allowing the claims under *Advanced Bionics* step 2 (i.e., *Becton* factors (c), (e), (f)) for at least three reasons. Pet. 7-8; see *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 4-7 (P.T.A.B. May 19, 2025) (precedential as to section A).

First, in contrast to *Empower*, BPI ***does not even argue*** that the Examiner erred nor does it address the Examiner's Reasons for Allowance at all (factor (e)). See *Empower*, IPR2025-01024, Paper 15 at 3 (rejecting as unpersuasive *Empower's* “argument that the Office erred during examination of the” ’780 patent). BPI's complete silence weighs strongly against institution. See *Vestas-Am. Wind Tech., Inc. v. Gen. Elec. Co.*, IPR2018-01029, Paper 9 at 14-15 (P.T.A.B. Oct. 19, 2018) (petitioner's failure to “point[] to error by the Examiner or even address[] the findings made by the Examiner” weighed “strongly against instituting”).

Second, as explained in Section III, the Examiner rejected substantially the same arguments made now by Petitioner when evaluating Just (factor (c)). The Examiner 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 does not dispute or even

address that finding. The Examiner's reasoning applies with equal force to Petitioner's three asserted references. Here, the alleged lead compound (Alsina-Fernandez Example 2) must be modified in specific ways in view of DiMarchi and Lau, and ***no other changes can be made***. Like the Examiner noted for Just, a skilled artisan here still "would have to choose options" for multiple positions within Example 2 without any teaching or motivation to choose the claimed options. *See id.*, 28. And as the POPR will further discuss, a skilled artisan would have had to make ***additional*** replacements and make one specific choice out of many, and no others, for numerous aspects of each compound to arrive at the claimed compounds.

Third, Petitioner offers no other evidence or facts warranting reconsideration (factor (f)). *See Nespresso USA, Inc. v. K-Fee Sys. GmbH*, IPR2021-01222, Paper 9 at 26-27 (P.T.A.B. Jan. 18, 2022). As explained, Petitioner's asserted references are not new. Though Petitioner seeks a do-over, the law is clear: 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. Because there is no material error, denial is warranted.

VI. THE PETITION'S WEAK MERITS WARRANT DENIAL

The Petition's weak merits—which Lilly's POPR will address more fully—also warrant denial. Obviousness challenges to chemical compound patents are evaluated using the lead compound test. *See Otsuka Pharm. Co. v. Sandoz, Inc.*, 678

F.3d 1280, 1290-93 (Fed. Cir. 2012). First, the Board determines whether a skilled artisan “would have selected the asserted prior art compounds as lead compounds, or starting points, for further development efforts.” *Id.* at 1291. It then assesses whether the prior art provided “a reason or motivation to modify a lead compound to make the claimed compound with a reasonable expectation of success.” *Id.* at 1292. The Petition fails to meet all requirements of this test and should be denied.

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). But while Petitioner concedes that GIP/GLP-1 dual agonists “were disclosed in a number of references,” it improperly limits its analysis to *only* Alsina-Fernandez's compounds. Pet. 34. Petitioner does not even *attempt* to show why a skilled artisan would have chosen Example 2 of Alsina-Fernandez over any of the numerous GIP/GLP-1 dual agonists disclosed in other prior art references. For instance, Petitioner disregards other GIP/GLP-1 dual agonists from references it identifies, such as DiMarchi and Finan (Ex. 1061), and ignores additional GIP/GLP-1 dual agonists from references cited on the patent's face, such as Just and DiMarchi '807. Pet. 34. Further, its expert fails to provide *any* reason a skilled artisan would choose Alsina-Fernandez for the

lead compound selection over *any* other reference disclosing GIP/GLP-1 dual agonists. Therefore, 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.

But even if Petitioner had not erroneously 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. And Petitioner ignores Alsina-Fernandez’s express teaching that Example 4 is its “most preferred embodiment.” *Id.*, 3:25-32. Petitioner’s failure to acknowledge these teachings exposes the true motivation behind its lead compound selection.

The real reason Petitioner focuses on Alsina-Fernandez Example 2 to the exclusion of other compounds is transparent: Petitioner engages in a hindsight-

driven selection based on “mere structural similarity” to the claims. *See Otsuka*, 678 F.3d at 1292. But the law is clear: “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 lead comes from one and only one place: the claims themselves. And worse, the only “functional properties” of Example 2 that Petitioner discusses are hindsight-driven and cherry-picked. Not only does Petitioner fail to consider compounds outside of Alsina-Fernandez, it ignores unfavorable data on its chosen lead compound.

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

Petitioner fails to cite a single case applying a lead compound analysis to invalidate a novel pharmaceutical compound. This is no surprise—Lilly’s research yielded only *three such cases ever*. In the first, *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, the claimed compound required only one modification from the prior art and patent owner’s expert testified in support of the lead compound selection and proposed modification. 752 F.3d 967, 969-70, 974-75 (Fed. Cir. 2014). In the other two, the claimed compound differed from the prior art by only a single isotopic substitution, and the art taught isotopic substitution of the lead compounds. *Alzheon Inc. v. Risen (Suzhou) Pharma Tech Co.*, IPR2021-00347, Paper 53 at 5, 53-55, 66 (P.T.A.B. July 12, 2022), *aff’d*, 2024 WL 1026081 (Fed.

Cir. Mar. 11, 2024); *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.*, 2023 WL 5370639 (Fed. Cir. Aug. 22, 2023).²

This case is nothing like those. Petitioner provides a legally deficient analysis of its lead compound selection. *Supra* Section VI.A. Further, hindsight would have been necessary to make the numerous substantial modifications to arrive at the claimed compounds. An unpatentability conclusion here would be unprecedented.

VII. PRIOR IPR CHALLENGE WARRANTS DENIAL

Finally, the Petition should be denied because it essentially replicates Empower's Petition, which was denied "based on a holistic assessment" of a nearly identical record. *Empower*, IPR2025-01024, Paper 15 at 3. "Even absent road mapping, prior challenges weigh against institution." *Treasure Garden, Inc. v. ATLeisure, LLC*, IPR2025-01005, -01006, Paper 11 at 3 (P.T.A.B. Oct. 3, 2025).

² Empower's unsuccessful opposition 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 (JLL), 2013 WL 12158369, at *1 (D.N.J. Mar. 26, 2013).

The redundancy of BPI's and Empower's Petitions is striking: BPI challenges a subset of the same claims that Empower challenged, and both Petitions include one obviousness ground combining Alsina-Fernandez as the lead reference and Lau as one of two secondary references. BPI concedes the parallels, "us[ing] the same exhibit numbering scheme as used in IPR2025-01024 for the same exhibits" "[f]or ease of reference." Pet. iii n.1. Further, BPI's expert admits to reviewing Empower's Petition and expert declaration, agreeing with and adopting parts of Empower's expert's analysis. Ex. 1084 ¶ 263. Though BPI substitutes DiMarchi for Just, the challenge here is equally weak and should be rejected.

At bottom, BPI attempts to take a second shot at Lilly's tirzepatide patent. But petitioners should not be allowed to use existing petitions as a blueprint, make non-material changes, and file repeated challenges against a patent. This practice undermines the integrity and efficiency of the Board, placing an undue burden on Board resources and diverting attention from new, potentially more meritorious cases. It also creates uncertainty and instability for patent owners, who deserve to rely on the finality of granted patents, particularly for patents with "strong settled expectations," as in this case. *Empower*, IPR2025-01024, Paper 15 at 2.

VIII. CONCLUSION

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

Respectfully submitted,

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.6(e), I certify that on this 14th day of October, 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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