

Case No. PGR2025-00057

Patent No. 12,234,236

UNITED STATES PATENT AND TRADEMARK OFFICE

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BEFORE THE PATENT TRIAL AND APPEAL BOARD

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CONJUPRO BIOTHERAPEUTICS, INC.,  
Petitioner,

v.

ASCLETIS PHARMA CHINA CO. LTD.,  
Patent Owner.

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Case No. PGR2025-00057

Patent No. 12,234,236

Title: GLP-1R agonist and therapeutic method thereof

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**PATENT OWNER'S PRELIMINARY RESPONSE**

*37 C.F.R. § 42.107*

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## I. INTRODUCTION

The Petition is not a genuine challenge to the validity of the claimed compounds but rather a calculated maneuver following Petitioner's unsuccessful attempt to obtain a license. The timing is telling: Petitioner initiated this proceeding only after Ascletis refused its unsolicited request to license the Challenged Patent, prompted by Petitioner's active development of oral GLP-1 agonists. Even more revealing, Petitioner filed its own patent application with a *later priority date*, directly claiming one of the compounds that it now attacks as "obvious." (EX2004; EX2005 (certified translation), 1, 95-96). Petitioner omitted this critical fact from the Petition, presumably because it shows Petitioner thought the claimed compounds were novel and non-obvious, at least until Ascletis's pioneering work became public. Now, having realized Ascletis invented the claimed compounds first, and unable to obtain a license, Petitioner has suddenly changed its tune and now asserts the claimed compounds were obvious all along.

Consistent with that change in heart, the Petition reads like a post-hoc analysis of how a skilled artisan *could have* arrived at the claimed compounds with the challenged patent in hand. The Petition asks the Office to find the challenged claims unpatentable based on cherry-picked compounds from the prior art that could only be selected using impermissible hindsight. Precisely because of the danger of hindsight, the Federal Circuit has held that it is "necessary to identify *some reason*

that **would have** led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007) (emphasis added). The Petition does not come close to meeting that burden.

Petitioner does not identify a single shortcoming of orforglipron or identify a problem to solve, much less one that would motivate a skilled artisan to make the changes needed to arrive at the claimed compounds. Indeed, far from suggesting the required changes, Petitioner’s primary reference, Yoshino, teaches away from the modification required in all the claimed compounds, replacing the methyl on the orforglipron indazole moiety with a cycloalkyl. Petitioner’s other references are cherry-picked out of a sea of prior art with only hindsight as a guide. Su, for instance, is but one of numerous references disclosing orforglipron derivatives and has no activity data for any of its compounds. Even worse, the Petition selects the only two compounds in Su with a cycloalkyl substitution (out of the more than 200 compounds disclosed), despite the lack of any data of any type for those two compounds. Similarly, Talele is one of many medicinal chemistry “review articles” touting the generic potential benefits of a particular substituent and has nothing to do with orforglipron. No skilled artisan would have picked these references – out of many possibilities – without having the challenged patent in hand to use as a roadmap. The references, thus, cannot establish the required motivation.

The Petition similarly comes up short on the other elements required to show obviousness. The Petition does not substantively address reasonable expectation of success, including only two conclusory sentences on that issue. Likewise, the Petition fails to address objective indicia of non-obviousness, despite conspicuous evidence of unexpected results in the specification of the challenged patent.

At bottom, the Petition fails to establish multiple elements required for obviousness and cannot show it is more likely that any of the challenged claims are unpatentable. Petitioner's request for post-grant review should be denied.

## **II. BACKGROUND**

### **A. Obesity and GLP-1R Agonists**

Obesity is a chronic disease that has become a major public health concern in recent years, affecting more than 800 million people worldwide. (EX2016, 1.) In the United States, approximately 42% of adults have obesity, and obesity-related costs are estimated at \$173 billion annually. (*Id.*) Obesity is a multifaceted and diverse condition that affects more than just an individual's weight. (*Id.*) Obesity can have significant negative impacts on health, including increasing the risk of life-threatening conditions such as type 2 diabetes, cardiovascular disease, fatty liver disease, and cancer, among many others. (*Id.*)

Over the last decade, glucagon-like peptide-1 receptor agonists have changed the treatment paradigm for obesity. (*Id.*, 2.) Glucagon-like peptide-1 ("GLP-1") is

a naturally occurring hormone, secreted in the gut in response to a meal, that reduces appetite and promotes feelings of fullness. (*Id.*, 2-3.) GLP-1 achieves these effects by binding to the GLP-1 receptor (“GLP-1R”), a protein found in the pancreas, brain, and other organs that plays a crucial role in regulating blood sugar levels, appetite, and other metabolic processes. (*Id.*, 2.)

GLP-1R agonist drugs work by mimicking the GLP-1 hormone and binding to GLP-1R. (EX2017, 2.) They result in reduced appetite, increased feelings of fullness, and delayed stomach emptying, leading to significant and sustainable weight loss of at least 15% for many patients. (*Id.*, 4-5.) At the time of the invention, two GLP-1R agonists (liraglutide (Saxenda®) and semaglutide (Wegovy®)) had been approved for chronic weight management in obese patients. (EX2017, 2; EX1001, 2:6-11.) However, both of those drugs are peptides that typically must be administered by subcutaneous injection. (EX2017, 2.)

At the time of the invention, scientists were also studying several small-molecule GLP-1R agonists for oral administration. (EX2017, 2; EX1001, 2:11-12.) One particularly promising small molecule candidate was orforglipron. (EX2017, 2.) Orforglipron is a once-daily, oral nonpeptide GLP-1 receptor agonist that Eli Lilly is developing for weight management and the treatment of type 2 diabetes. (*Id.*) By 2023, it was known that orforglipron has “GLP-1 receptor agonistic activity comparable or even stronger than GLP-1 derivatives.” (EX1010,

4; Pet. 9 (“Orforglipron exhibits full agonist activity, promoting cAMP accumulation to levels comparable to native GLP-1, with EC<sub>50</sub> values of 1.1 nM for both human and cynomolgus monkey GLP-1 receptors.”).) Orforglipron was also known to have a favorable pharmacokinetic profile that supports once-daily oral administration. (EX2017, 2.) Indeed, as Petitioner explains, “[u]nlike traditional peptide-based GLP-1R agonists, orforglipron was *structurally optimized* for once-daily oral administration, addressing compliance issues associated with injectable therapies for type 2 diabetes and obesity.” (Pet. 1-2 (emphasis added).)

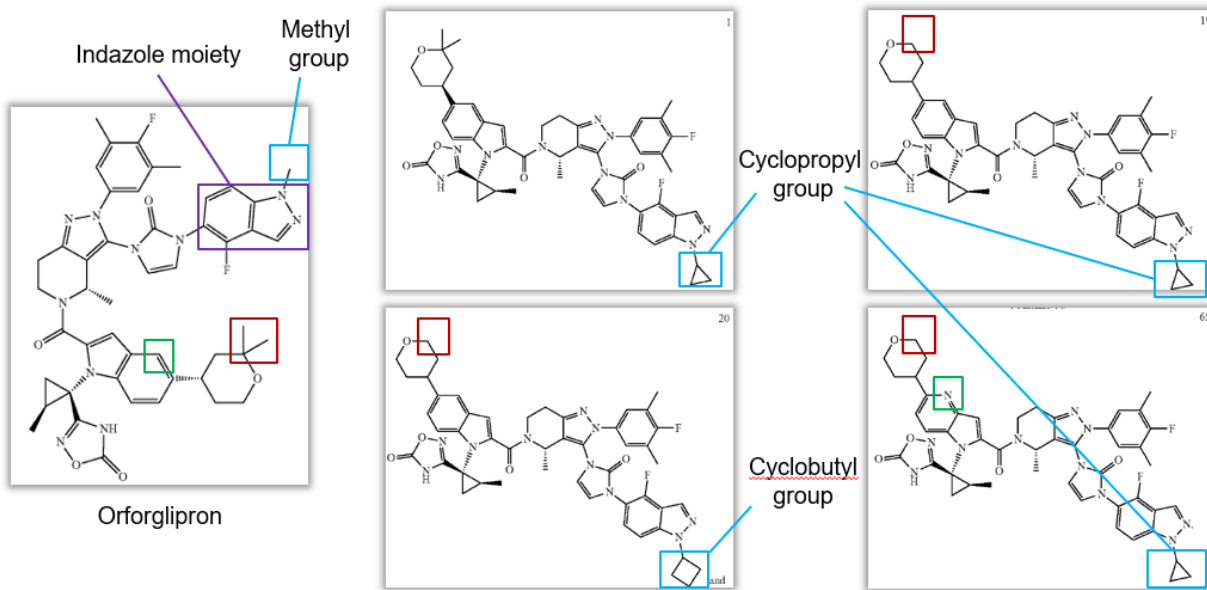
By 2023, Phase 2 clinical trials showed that daily oral orforglipron caused weight reduction and related benefits similar to that observed with the injectable GLP-1 receptor agonists already approved for weight management. (EX2017, 7.) Following successful Phase 2 trials, Eli Lilly initiated a Phase 3 study to evaluate the safety and efficacy of once-daily oral orforglipron in patients with obesity. (EX2018.) The study remains ongoing. (*Id.*)

**B. The Challenged Patent Discloses and Claims Novel GLP-1R Agonists with Improved Properties**

Despite the success of orforglipron, the inventors had the insight to try to discover even better small molecule GLP-1R agonists. After considerable trial and error, the inventors developed oral small molecule GLP-1R agonists with unexpectedly superior properties. (EX1001, Abstract, 4.) The challenged patent

discloses over 60 novel compounds that maintain the core structure of orforglipron but have one or more modifications, resulting in unexpected improved properties. (EX1001, 167:38-200:48.) The challenged claims cover seven of the disclosed compounds: Compounds 1, 13, 18, 19, 20, 21 and 65. (EX1001, 204:10-220:58.)

Petitioner only argues that four of the claimed compounds, Compounds 1, 19, 20 and 65, would have been obvious. (Pet. 1-4.) Compared to orforglipron, all four challenged compounds have a cyclopropyl or cyclobutyl substituent in place of the methyl group on the indazole moiety of orforglipron, and Compounds 19, 20 and 65 also have one or more additional modifications, as shown below.



(EX1008, 99 (annotated); EX1001, 205:1-206:66 (annotated).)

Even one change to a molecule can make big changes to the molecule's properties. *Takeda Pharm. Co. Ltd. v. Torrent Pharms. Ltd.*, 844 F. App'x 339, 341

(Fed. Cir. 2021) (“[I]n the relevant art of pharmaceutical development, very small changes in molecular structure can have dramatic effects on the properties of the molecule.”). That is the case here. The challenged patent discloses unexpectedly improved properties for the claimed compounds. (EX1001, 199:50-203:67.) In particular, the specification discloses the results of an in vitro activity study with EC<sub>50</sub> values for the claimed compounds, including results as low as 0.012 nM. (*Id.*, 201:1-27, Table 2.) The specification also includes the results of two studies comparing the pharmacokinetics of the claimed compounds to orforglipron. (*Id.*, 201:31-202:50, Tables 3-4.) Compound 19, for instance, demonstrated a C<sub>max</sub> more than five times greater than orforglipron and an AUC<sub>0-48</sub> more than eight times greater. (*Id.*, 202:45.)

Ascletis is developing one of the claimed compounds, named ASC30, for treatment of obesity. (EX2022.) In vitro, ASC30 has demonstrated high potency with more than double the activity of orforglipron. (EX2023.) In Phase 1 studies, ASC30 showed promising efficacy and safety data, including a superior pharmacokinetic profile and a 6.5% mean reduction in body weight after just 28 days of treatment. (EX2022, 2.) Ascletis is currently conducting Phase 2 trials on ASC30 with topline results expected later this year. (*Id.*, 3.)

**C. The Prior Art Identifies Innumerable Potential Modifications to Orforglipron**

The inventors' road to the Claimed Compounds was far from obvious, in part because there were innumerable potential and unpredictable modifications that could be made to numerous positions on the core structure of orforglipron.

Orforglipron was first disclosed in the patent applications that led to Petitioner's Yoshino reference. The Examiner expressly considered Yoshino, and allowed the Challenged Claims over it, in the Notice of Allowance. (EX2002, 845.) Yoshino discloses a generic structure of GLP-1R agonist compounds that allows for hundreds, if not thousands, of potential substitutions and encompasses millions of potential compounds. (EX1008, 3:1-6:2.) In addition to orforglipron, Yoshino discloses at least 158 additional exemplary compounds that include various modifications to the orforglipron core structure, including various substituents on the indazole moiety. (*E.g., id.*, Example Compounds 16, 126, 28, 26, 17, 120, 119, and 30.) Notably, despite the plethora of potential substitutions it discloses, Yoshino's generic structure ***does not allow for a cyclopropyl or cyclobutyl substituent*** on the indazole moiety and none of the exemplary compounds include one either. (*Id.*, 5:21-67.)

Su is another reference that discloses small molecule oral GLP-1R agonists. (EX1007, 4:10-40.) Su includes a broad generic structure with hundreds of options

for substituents, likely encompassing millions of potential compounds. (*Id.*, 5:1-7:4.) Su also discloses at least 218 working examples with various modifications to the core structure of orforglipron. (*Id.*, 97:7-289:23.) In just those examples, Su discloses hundreds of potential modifications that could be mixed and matched to create innumerable potential compounds. (*Id.*) Su does not disclose biological activity data for any compound but does disclose pharmacokinetic data for five of its 218 working examples, none of which are the compounds relied on by Petitioner. (*Id.*, 294:29-295:1.)

Numerous other references not relied on by Petitioner also show potential modifications to the orforglipron core structure. In fact, the Examiner's search report – based on the core structure of orforglipron – returned 39 references with 529 pages of orforglipron derivatives, illustrating the plethora of potential modifications to orforglipron. (EX2002, 312-839; Pet. 11.) For example, WO 2024/169,952 (“Huang”) discloses 238 exemplary orforglipron derivatives with extensive data on the biological activity, half-life, potency, permeability, exposure, and solubility of those compounds. (EX2019, [1496]-[1519].) WO 2023/016,546 (“Meng”) discloses 150 additional orforglipron derivatives with biological activity for those compounds, as well as rat PK studies and glucose tolerance tests in non-human primates. (EX2020, 206:14-213:8.) WO 2024/153,070 (“Xu”) discloses yet another 63 exemplary orforglipron derivatives with biological activity data.

(EX2021, [251]-[253].) These examples provide just a sampling of the many references disclosing orforglipron derivatives (many with more available data than Su) and the wide numerous routes that a skilled artisan seeking to modify orforglipron could have followed.

**D. Petitioner Filed a Patent Application with a Later Priority Date Claiming the Same Compounds It Now Says Are Obvious**

Despite now claiming that the inventors' novel GLP-1R agonists would have been obvious, Petitioner filed a patent application that claims one of the exact same compounds as the Challenged Claims. On December 22, 2023, three months after the earliest priority date for the Challenged Patent, real party-in-interest CSPC filed a Chinese provisional application that later published as WO 2025/131,043. (EX2005, 1.) The PCT publication discloses and individually claims Compound 1, one of the compounds that Petitioner now says would have been obvious as of an even earlier priority date. (EX2005, 95-96 (Compound 10 of Claim 10).) As shown above, Compound 1 differs from orforglipron by the replacement of the methyl group on the indazole moiety with a cyclopropyl group. (*See supra* Section II.C.) Thus, before filing this Petition, Petitioner did not believe that substitution was obvious, but has now changed course and argues claimed compound 1 is obvious.

**III. CLAIM CONSTRUCTION**

The Board “need only construe terms ‘that are in controversy, and only to the extent necessary to resolve the controversy.’” *See Nidec Motor Corp. v. Zhongshan*

*Broad Ocean Motor Co. Ltd. Matal*, 868 F.3d 1013, 1017 (Fed. Cir. 2017).

Petitioner does not seek Board construction of any terms. (Pet. 45.) Ascletis does not believe the Board needs to construe any terms to resolve the controversy by denying the Petition. Ascletis reserves the right to propose constructions for terms of the Challenged Claims should the Board institute trial.

#### **IV. PETITIONER’S GROUNDS 1 AND 2 FAIL**

Ground 1 relies on “Su, Yoshino, and Kawai, in view of Talele,” and Ground 2 relies on “Yoshino and Kawai in view of Talele.” (Pet. 7.) In both grounds, Petitioner asserts that a skilled artisan would have modified orforglipron to arrive at claimed Compounds 1, 19 and/or 20. (Pet. 53, 62, 94-95, 98-99.) But the Petition fails to provide a specific rationale for making any modification to orforglipron, much less one that would lead to the precise modifications at the specific locations reflected in the claimed compounds, all while ignoring the overwhelming number of other potential modifications described in the art. Petitioner’s alternative argument (for only Compound 19), which uses Compound 175 of Su as a lead, fares no better because Petitioner has failed to show that a skilled artisan would have picked that compound for further development out of the sea of prior art. In addition, no matter the starting point, the Petition fails to provide any substantive analysis of reasonable expectation of success, barely giving lip service to that requirement with only two

conclusory sentences, and does not address objective evidence at all. Petitioner thus fails to meet its burden at each step of the obviousness inquiry.

**A. Petitioner Fails to Articulate a Motivation to Modify Orforglipron that would Lead to the Claimed Compounds**

Petitioner does not show it would have been obvious to modify orforglipron to arrive at the claimed compounds. While “[a]ny compound may look obvious once someone has made it and found it to be useful, working backwards from that compound, with the benefit of hindsight . . . does not render it obvious.” *Sanofi-Aventis U.S., LLC v. Dr. Reddy’s Lab’ys, Inc.*, 933 F.3d 1367, 1375 (Fed. Cir. 2019). To avoid the risk of hindsight bias, a challenger must “identify some reason that would have led a chemist to modify a known compound in a particular manner to establish prima facie obviousness of a new claimed compound.” *Takeda Chem. Indus., Ltd.*, 492 F.3d at 1357; *see also Cytiva BioProcess R&D AB v. JSR Corp.*, 122 F.4th 876, 885-86 (Fed. Cir. 2024).<sup>1</sup>

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<sup>1</sup> Petitioner appears to specifically rely on a lead-compound theory in the Petition. (*See, e.g.*, Pet. 3, 20, 29, 30, 53, 62, 94-95, 98-99.) However, even if the Petition could be read to advance an obvious-to-try rationale, for the same reasons articulated below, Petitioner does not come close to showing that there was “a design need or market pressure to solve a problem” or that there were “a finite number of identified, predictable solutions.” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-22 (2007).

Petitioner does not come close to meeting that burden. Petitioner does not identify a single reason a chemist would seek to modify orforglipron at all and, instead, does no more than cherry-pick potential modifications from the prior art with no stated goal, arriving at the claimed compounds through pure hindsight. For that reason alone, the Board should not institute based on Grounds 1 and 2.

**1. The Petition Fails to Identify Any Specific Reason to Modify Orforglipron**

The Petition does not provide any specific reason to modify orforglipron or identify any shortcoming that a chemist would have been motivated to improve that would have led to the claimed compounds. *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th, 882, 887-88 (Fed. Cir. 2024) (reversing the Board’s finding of obviousness where “[t]he petition does not argue [prior art] articulates any reason to substitute one for another or any advantages that would flow from doing so”).

The Petition, instead, does no more than sing the praises of orforglipron. As the Petition concedes, at the time of the invention, it was “well known” that orforglipron was “orally bioavailable” and “exhibited full agonist efficacy . . .

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To the contrary, the Petition fails to identify any problem a skilled artisan would seek to solve, and the Petition itself shows that there were innumerable ways a skilled artisan could have attempted to modify orforglipron, all in an unpredictable field.

comparable to native GLP-1.” (Pet. 1-2, 9.) The Petition also admits that orforglipron was “structurally optimized” for “once daily oral administration.” (Pet. 1, 9.) And, as of 2023, Phase 2 clinical trials had shown that orforglipron “significantly improve[d] glycemic control and reduces body weight.” (Pet. 10; EX1002, ¶51; EX1010, 4; EX1012, 2.) As of the priority date, this “promising candidate” was in Phase 3 clinical studies and had “the potential to transform treatment paradigms for patients with type 2 diabetes and obesity.” (EX1002, ¶51; Pet. 9-10; EX1012.) Thus, far from providing a specific reason to modify orforglipron or identify a problem a skilled artisan would try to solve, the Petition simply touts the benefits of the drug.

The Petition, in fact, does not identify a single shortcoming of orforglipron or identify any specific property that a skilled artisan would seek to change or improve. Instead, Petitioner generically argues that a skilled artisan *generally* would “have been aware of various modifications to *drug molecules* that could improve metabolic stability, modulate biological activity of drug molecules, and/or improve molecular, physicochemical, and pharmacokinetic properties. (Pet. 53 (emphasis added).) Based on that general knowledge, a skilled artisan “*seeking to modify orforglipron* would have therefore been motivated to introduce peripheral modifications to improve or optimize *certain properties*, while maintaining the core scaffold of the molecule to preserve activity.” (Pet. 53; EX1002, ¶152 (emphasis

added).) In other words, Petitioner’s argument is that a skilled artisan would be generally motivated to make any change to orforglipron that could be beneficial in any way. Such generic and circular reasoning is insufficient to establish the motivation required to prove obviousness. *See Takeda Pharm. Co. Ltd. v. Torrent Pharms. Ltd.*, 844 F. App’x 339, 342 (Fed. Cir. 2021) (rejecting the challenger’s argument that “because the skilled artisans are medicinal chemists who are ‘always looking for a novel compound,’ the skilled artisan would have been motivated to [make the modification]”); *see also Amerigen Pharms. Ltd. v. UCB Pharma GmbH*, 913 F.3d 1076, 1089 (Fed. Cir. 2019) (“A general motivation to modify [the lead compound] based on a prior patent would not suffice.”); *Otsuka Pharm. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1292-93 (Fed. Cir. 2012) (“Again, pertinent properties guide the analysis, for ‘it is the possession of promising useful properties in a lead compound that motivates a chemist to make structurally similar compounds.’”).

Petitioner also cannot establish obviousness by arguing that a skilled artisan would not expect the modifications reflected in the claimed compounds to make the properties worse. (*See, e.g.*, Pet. 50-51 (modifications to the indazole moiety “would not be expected to cause **significant structural disturbance** to the ligand-binding pocket, and thus likely would **maintain binding potency**”) (emphasis added); Pet. 59 (“Yoshino further corroborates this understanding because it shows that substitution of the methyl group with a tetrahydrofuran ring yields compounds

*retaining biological activity.*”) (emphasis added).) The Federal Circuit has made clear that a patent challenger must establish an affirmative reason for a chemist to make a modification, not merely point to all modifications that may look “safe” in hindsight. *Sanofi-Aventis*, 933 F.3d at 1379 (finding no motivation where “no cited reference shows that [the substitutions] have improved properties” and rejecting the argument that a POSA “would have made [the substitutions] because they are ‘small, conservative changes’”). Petitioner provides no such affirmative motivation.

Petitioner’s failure to articulate a specific problem that the skilled artisan would have tried to solve shows that its selection of prior art references is no more than improper hindsight and is reason alone to reject Grounds 1 and 2.

**2. Petitioner Provides No Motivation to Replace the Methyl on the Indazole Moiety with Cyclopropyl or Cyclobutyl**

Petitioner further does not articulate a reason why a skilled artisan would be motivated to make the specific modifications to orforglipron reflected in the claimed compounds. *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020) (“The obviousness inquiry does not merely ask whether a skilled artisan *could* combine the references, but instead asks whether ‘they *would have been motivated* to do so.’”) (emphasis added). In particular, the Petition does not establish a motivation to

replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl or cyclobutyl.<sup>2</sup> That failure alone is fatal to Grounds 1 and 2.

**Yoshino.** Yoshino fails to disclose a cycloalkyl substituent on the indazole moiety and, in fact, teaches away from such a substitution.

Yoshino noticeably excludes cycloalkyl substituents from indazole moiety. Yoshino includes a single generic chemical formula of the invention, Formula (I). (EX1008, 3:1-6:2.). In Formula (I), position  $Z^2$  corresponds with the location of the indazole moiety in orforglipron. (*Compare* EX1008, 3:5-15 (Formula (I)) *with* EX1008, 99 (Example Compound 67).) Yoshino provides that  $Z^2$  can be optionally substituted with one to five substituents selected from eleven broad categories, most of which include numerous options. (EX1008, 5:21-67.) In all, there are hundreds, if not thousands, of potential substituents identified for  $Z^2$ , including “C<sub>1-6</sub> alkyl” and

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<sup>2</sup> Because all the claimed compounds require a cyclopropyl or cyclobutyl substitution on the indazole moiety, we focus in this response on the Petition’s failure to show a motivation to make that change. If the Board institutes trial, Ascleitis will show that none of the substitutions reflected in the claimed compounds were obvious, much less in combination, as in several of the claimed compounds.

“3-12 membered heterocycle.”<sup>3</sup> (*Id.*, 5:21-22.) Despite its breadth, Yoshino’s list of allowed substituents at  $Z^2$  ***excludes cycloalkyls***, even though that type of substitution is allowed for other positions in Formula (I). (*E.g.*, *id.*, 3:51-54 (“ $R^7$  and  $R^8$  . . . optionally substituted with . . .  $C_{3-15}$  cycloalkyl”).) Consistent with its exclusion from Formula (I), Yoshino includes 159 exemplary compounds. (*Id.*, 31-55, 89-90, 92-101, 120-121, 133-161.) Several of those compounds include substituents other than methyl on the indazole moiety but not even one includes a cycloalkyl. (*E.g.*, *id.*, Example Compounds 16, 126, 28, 26, 17, 120, 119, and 30.) Yoshino’s deliberate exclusion of cycloalkyl substituents at  $Z^2$  teaches away from the claimed compounds. *Eli Lilly and Co. v. Zenith Goldline Pharms., Inc.*, 471 F.3d 1369, 1378 (Fed. Cir. 2006) (concluding that a prior art patent’s preference for halogen containing compounds taught away from using a non-halogenated compound as a substituent).

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<sup>3</sup> Neither of those terms include cycloalkyl groups (such as cyclopropyl or cyclobutyl). (*Id.*) In its “Definition” section, Yoshino defines “ $C_{1-6}$  alkyl” as “a straight chain or branched chain alkyl group with 1 to 6 carbons” and “heterocycl[e]” as “a non-aromatic cyclic group comprising one or more hetero atoms selected from nitrogen, oxygen and sulfur atoms, and it may be completely saturated or partly unsaturated.” (EX1008, 9:57-58, 10:39-42.)

While ignoring Yoshino's teaching away, Petitioner incorrectly argues that structures with a tetrahydrofuran ("THF") ring on the indazole moiety encourage the use of "ring structures" generally. (*E.g.*, Pet. 23.) But the THF examples further point the skilled artisan away from cycloalkyl groups. First, THF rings include an oxygen atom which makes the group moderately polar, whereas cycloalkyls contain only carbon and hydrogen atoms and are non-polar. (*Contrast EX2024 with EX2025.*) Skilled artisans would not expect a polar THF ring to have the same effect on a molecule as a non-polar cycloalkyl. (EX2026, 2; EX2027, 2-6.) Second, even if they were comparable, all of the compounds with a THF substitution have less activity than orforglipron. (*See EX1008, 162-63 (contrast Compound 8 (2.5 nM), Compound 14 (2.3 nM), Compound 22 (2.3 nM), Compound 40 (2.2 nM), and Compound 64 (2.0 nM) with Compound 67 (1.2 nM)).*) Indeed, the substitution of a THF group for the methyl group in orforglipron resulted in a nearly two-fold decrease in activity (*See id. (contrast Compound 67 (1.2 nM) with Compound 40 (2.2 nM)).*) Petitioner does not explain why a skilled artisan would seek to make a modification that led to compounds with lower activity. Moreover, numerous other compounds in Yoshino have up to four times **greater activity** than the THF-containing compounds. (*See id. (Compound 16 (0.51 nM), Compound 26 (0.77 nM), Compound 31 (0.74 nM), Compound 32 (0.94 nM)).*) Petitioner does not explain why a skilled artisan seeking to modify orforglipron would look to the THF-

containing compounds, while ignoring other Yoshino compounds up to four times more potent. Like the rest of the petition, the only reason is impermissible hindsight.

**Kawai.** Kawai does not disclose or suggest substituting a cycloalkyl for the methyl group on the indazole moiety of orforglipron. In fact, Kawai merely provides a structural analysis of orforglipron binding to the GLP-1 receptor and does not suggest making any changes to the structure of orforglipron. (EX1004, 2-4.)

Petitioner's expert, without support, interprets Kawai to "suggest[] that the [GLP-1 binding] pocket could reasonably accommodate a compound bearing a bulkier substituent in place of the methyl group [on indazole]." (EX1002, ¶58.) Even if that read of Kawai was correct (it is not), that the binding pocket "could" reasonably accommodate a bulkier substituent does not provide a reason a skilled artisan "would" be motivated to make that modification. *Adidas*, 963 F.3d at 1359. Moreover, it provides no reason to select a cyclopropyl or cyclobutyl substituent from the universe of possible "bulkier substituents" nor suggests what effect those substituents would ultimately have on the compound.

**Talele.** Despite Yoshino's teaching away and Kawai's silence, Petitioner incorrectly contends that Talele would motivate a skilled artisan to replace the methyl on the orforglipron indazole moiety with cyclopropyl. (Pet. 61-62, 92-94.) But Talele has nothing to do with anti-GLP1 compounds, generally, or orforglipron, specifically. (EX1009.) Instead, as Petitioner concedes, Talele is a "review article"

that discusses the use of cyclopropyl groups in medicinal chemistry since the 1960s in completely unrelated drug products designed to treat conditions as diverse as cancer, HIV, arthritis and depression. (Pet. 2, 35-38; EX1009, 2-6, 11, 16-17, 21-23.) Talele says nothing about the use of cyclopropyl groups in GLP-1R agonists and does not indicate what effect cyclopropyl groups might have on such molecules or where on such a compound a cyclopropyl might be advantageous (if at all).

Given its complete lack of relevance to orforglipron, Petitioner's selection of Talele reeks of hindsight bias. *Sanofi-Aventis*, 933 F.3d at 1378 (rejecting obviousness challenge to claimed taxane compounds as "hindsight-driven" where the asserted references "did . . . not contemplate taxanes" and "investigated compounds . . . structurally very different from taxanes"). Indeed, there are numerous other prior art review articles that similarly (and generically) tout the potential benefits of using various substituents in medicinal chemistry (other than cycloalkyl) that would have been known to a skilled artisan. (EX2007, EX2008 (oxetanes); EX2009 (oxadiazoles); EX2010 (thiadiazoles); EX2011 (bicyclopentanes); EX2012 (nitrogen heterocycles); EX2013 (aromatic rings); EX2014 (8-11-membered rings); EX2015 (bicyclic rings).) Petitioner provides no reason why a skilled artisan would have selected Talele, as opposed to a generic review article on a different substituent. Again, the only reason is hindsight.

Indeed, Petitioner argues that Talele teaches that cyclopropyl groups can be used for “enhancing metabolic stability, improving pharmacokinetic properties, or modulating the biological activity of a drug molecule” (Pet. 62) but does not suggest that orforglipron has any problem or shortcoming with those properties.<sup>4</sup> Instead, the Petition indicates that orforglipron was “orally bioavailable,” “exhibited full agonist efficacy” and was “structurally optimized for once-daily oral administration.” (Pet. 1.) These are hallmarks of good metabolic stability, pharmacokinetics, and biological activity, not suggestions of need for improvement.

Talele, in sum, does not disclose anything about orforglipron and does not provide any motivation to make the changes required for the claimed compounds.

**Su.** Petitioner also fails to show that Su (asserted only against claimed Compound 19) would motivate a skilled artisan to replace the methyl on the indazole moiety of orforglipron with cyclopropyl.

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<sup>4</sup> Even if Petitioner had articulated a metabolic or pharmacokinetic issue with orforglipron, a skilled artisan would have no way to know if adding a cyclopropyl (much less at a specific position on the molecule) would improve those characteristics. Talele itself discusses cases where replacement of methyl with cyclopropyl does not lead to improved properties. (*E.g.*, EX1009, 24.)

Su is one of numerous references disclosing potential modifications to the orforglipron core structure. (EX1007, 97:7-289:23.) As explained above, the Examiner's search report, by itself, resulted in 39 references disclosing orforglipron derivatives, many of which included biological activity data. (*See supra* Section II.C; Pet. 11 (Examiner's search report "identified hundreds of compounds from dozens of references.") Petitioner provides no reason why a skilled artisan would pick Su out of that sea of prior art, particularly given that it does not include any biological activity data for any compound. *AstraZeneca AB v. Zydus Pharms. (USA) Inc.*, 2021 WL 4819905, at \*3 (D. Del. Oct. 15, 2021) (finding "a POSA would not have been motivated to [modify a prior art compound]" because of "the lack of biological activity data in [prior art reference]"), *appeal dismissed*, 2022 WL 17292025 (Fed. Cir. 2022).

Even if a skilled artisan picked Su out of a hat, Petitioner's reliance on Compounds 44, 175 and 176 is more blatant cherry picking. Su includes 218 exemplary compounds and has data (pharmacokinetic data) for only five of them, Compounds 1, 3, 64, 173, and 174, none of which are the compounds relied on by Petitioner. (EX1007, 294:29-295:1.) Petitioner does not even mention those compounds, likely because they do not have the indazole moiety of the claimed compounds, much less a cyclopropyl substitution. (EX1007, 97 (Compound 1), 98 (Compound 3), 150 (Compound 64), 243 (Compounds 173, 174).) Although Su

would only be found with hindsight in the first place, if a skilled artisan considered Su, they would focus on the compounds with data, not those relied on by Petitioner.

While ignoring the lack of data, Petitioner incorrectly argues that a skilled artisan would focus on Compounds 44, 175 and 176 because they are deuterated, stereoisomerically pure, and structurally similar to one another. (Pet. 3, 29, 52-53.) Petitioner cites nothing but the unsupported testimony of its expert for this trail of breadcrumbs theory. (*Id.*) But, even if Petitioner's theory were correct (and it is not), Petitioner and its expert merely argue this shows that *Su* considered Compounds 44, 175 and 176 to be "promising candidates." (Pet. 52; EX1002, ¶¶61, 149.) Even if Su was interested in those compounds (for some unknown reason), Su does not disclose any data for them – no biological data, no pharmacokinetic data, no stability data, nothing. (EX1007.) A skilled artisan would thus have no way to assess the effect of the substitutions made in those compounds relative to orforglipron.

In sum, a skilled artisan would have no reason to consider Su or the specific compounds in Su relied on by Petitioner without the use of impermissible hindsight. And, in any event, Su could not have motivated a skilled artisan to substitute cyclopropyl for methyl on orforglipron's indazole moiety given the complete lack of data on the Su compounds. *See Eli Lilly*, 471 F.3d at 1379 ("[T]he state of the art would have directed the person of ordinary skill in the art away from unfluorinated compounds . . . After all, the primary example . . . did not provide any biological

data for [the compound], suggested a preference for halogen-containing compounds, and identified a fluorine-containing compound . . . as ‘particularly active.’”).

Because Petitioner has failed to articulate any reason why a skilled artisan would have replaced the methyl group on the indazole moiety of orforglipron with cyclopropyl or cyclobutyl, Grounds 1 and 2 must fail.

### **3. Petitioner Ignores the Numerous Types and Locations of Potential Modifications to Orforglipron**

Petitioner further provides no reason why a skilled artisan would have made the modifications needed to arrive at the claimed compounds but ignored numerous other options. Petitioner’s own references and art cited during prosecution disclose a vast array of potential modifications to the core structure of orforglipron. (*See supra* Section II.C.) The only way Petitioner can jump from orforglipron to the claimed compounds is through “hindsight reconstruction . . . rather than a reasoned basis for” the modifications in the claimed compounds. *Sawai USA, Inc. v. Astellas Pharma Inc.*, IPR2018-00079, Paper 7, 24-25 (PTAB May 4, 2018).

First, the prior art discloses many possible locations where a skilled artisan could attempt to modify orforglipron. Kawai, for instance, identifies four different moieties of orforglipron that interact with the GLP-1 receptor. (EX1004, 3.) Petitioner argues (albeit, incorrectly) that Kawai shows that the GLP-1 receptor “could reasonably accommodate a compound bearing a bulkier ring substituent in

place of the methyl group” on indazole but does not explain why a skilled artisan would focus only on that position and not also consider substitutions on the other three moieties, without the use of hindsight. (Pet. 2, 35, 51.) Tellingly, the prior art discloses modifications to many positions on the orforglipron core structure, showing that skilled artisans had no such laser focus. (*See, e.g.*, EX1008, 100 (Compound 69), 101 (Compound 72); EX1007, 116 (Compound 31), 120 (Compound 40); EX2021, 47 (Compound 6), 48 (Compound 13).)

Second, even looking solely at the indazole moiety, the skilled artisan would have had an overwhelming number of options for potential substitutions. Yoshino alone discloses hundreds, if not thousands of potential substituents at the “Z<sup>2</sup>” position. (EX1008, 5:21-67; *see supra* Section II.C.) Other prior art references likewise disclose a wide array of potential substitutions that a skilled artisan could consider on the indazole moiety. (*See, e.g.*, EX1007, 254 (Compound 181), 255 (Compound 182), 272 (Compound 198); 273 (Compound 199); EX2020, 63 (Compound 112); EX2021, 53 (Compound 54).) And, unlike the references Petitioner relies on for cyclopropyl, many of these references actually have biological data for their compounds, giving skilled artisans some information about the substitutions’ effects. (*See, e.g.*, EX2019, [1496]-[1519]; EX2020, 206:14-213:8; EX2021, [251]-[253].) Petitioner provides no reason why a skilled artisan would choose cyclopropyl or cyclobutyl out of all these potential options.

Third, petitioner does not explain why a skilled artisan would be motivated to remove the methyl group on the indazole moiety, particularly given the known benefits of methyl groups in some compounds. (EX2028, 1-2.) A skilled artisan would have been aware of the so-called “magic methyl effect,” which refers to the outsized impact a single methyl group can have on a molecule’s potency, selectivity, conformation, and metabolism. (*Id.*, Abstract (“The ‘methylation effect,’ or the ‘magic methyl’ effect, is a factor that stands out due to the number of examples that demonstrate profound changes in either pharmacodynamic or pharmacokinetic properties.”).) Given the known impact of methyl groups, a skilled artisan would have been less likely to prioritize substituting the methyl group on indazole, as opposed to modifying other groups on orforglipron.

Where, as here, “the options of substituent and substituent position would not have been as narrow as those proposed by [Petitioner],” the Board has denied institution. *Par Pharm. Inc. v. Novartis AG*, IPR2016-00084, Paper 73, 35 (PTAB Jan. 11, 2018); *Mylan Pharms. Inc. v. UCB Pharma GmbH*, IPR2016-00514, Paper 38, 43 (PTAB July 19, 2017) (“The sheer number of possibilities for substitution narrows the possibility that one of ordinary skill in the art readily could have arrived at the specific [substituent].”); *Mylan Pharms. Inc. v. Novo Nordisk A/S*, IPR2023-00723, Paper 9, 44 (PTAB Oct. 2, 2023) (denying institution where “given the vast

number of potential GLP-1 modifications . . . Petitioner’s argument reduces to impermissible hindsight”). The Board should do so here as well.

**B. Petitioner Fails to Establish that Compound 175 of Su is a Proper Lead Compound**

As an alternative to starting with orforglipron, the Petition incorrectly argues for Ground 1 that Su’s “Compound 175 would have been reasonably considered by a POSA as a promising lead compound for further structural modification.” (Pet. 57.) Petitioner fails to establish that Compound 175 was a viable lead compound.

To satisfy the “lead-compound framework,” Petitioner must 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 (emphasis added) (affirming district court finding that challenger had not established prior art compound as proper lead because other compounds demonstrated greater potency and were more thoroughly studied than proposed lead compounds); *see also Sawai*, IPR2018-00079, Paper 7, 19-22 (denying institution where “Petitioner provides no persuasive explanation why a skilled artisan would have focused on pharmacophore A to the exclusion of pharmacophore B” for a lead). Here, a skilled artisan looking to develop an oral GLP-1 inhibitor would have had many candidates to choose from and no reason to pick Su Compound 175.

Petitioner, first, has failed to provide any reason why a skilled artisan would choose Su out of all the references related to GLP-1R agonists and orforglipron. As discussed above, Su is but one of many references disclosing small molecule GLP-1R agonists and/or orforglipron derivatives. (EX1007; *see supra* Section II.C.) Indeed, during prosecution, the Examiner's search based on the core structure of orforglipron resulted in 39 prior art references that disclosed orforglipron derivatives. (EX2002, 312-839.) In the context of this crowded field, Petitioner does not identify anything that makes Su stand out. Su does not even disclose ***activity data for any of its compounds***, leaving a skilled artisan to guess if its compounds are even viable.

Even considering Su, a skilled artisan would not have selected Compound 175 as a potential lead for further development. Indeed, Petitioner ignores that Su does not provide ***any data whatsoever*** on the properties of Compound 175. That alone makes its selection as a lead compound improper. *See Otsuka*, 678 F.3d at 1292 (“In determining whether [skilled artisan] would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound's pertinent properties . . . . Absent 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.”); *Daiichi*, 619 F.3d at 1353-54 (rejecting proposed

lead compounds where the art lacked data on their oral activity, binding affinity, intravenous activity, and selectivity, but included such data for other compounds).

Petitioner also fails to show that a skilled artisan “would have had a ***reason to select*** [Su compound 175] ***over*** [other compounds].” *Daiichi*, 619 F.3d at 1353-54 (upholding rejection of proposed “second-generation ARB” leads over “***other*** second-generation ARBs”) (emphasis added). Petitioner does not even acknowledge that Su provides pharmacokinetic data on five compounds, none of which is Compound 175. (EX1007, 294:29-295:1.) Petitioner provides no reason why a skilled artisan would select Compound 175 over those compounds in Su, much less other well-studied compounds in the prior art, ***including orforglipron***.

At bottom, Petitioner’s selection of Compound 175 of Su, out of all the compounds that one could select as a lead, is nothing but improper hindsight. *See Takeda Chem. Indus. Ltd.*, 492 F.3d at 1359-60 (upholding rejection of proposed lead where the “art disclose[s] a broad selection of compounds any one of which could have been selected as a lead . . . for further investigation” and district “court found nothing in the . . . art to narrow the possibilities... to [the proposed lead]”).

For this additional reason, Grounds 1 fails: “***Potent and promising activity in the prior art trumps*** mere structural relationships.” *Daiichi*, 619 F.3d at 1353-54 (emphasis added). Petitioner’s selection of Compound 175 amounts to nothing more

than picking a structure out of the prior art based on structural similarity with the challenged patent in hand.

**C. Petitioner Fails to Establish a Reasonable Expectation of Success**

Regardless of the starting point, Grounds 1 and 2 fail for an additional reason: the Petition fails to establish a reasonable expectation of success. As the Petition acknowledges, a prima facie case of obviousness requires a showing of reasonable expectation of success. (Pet. 45-46.) *Mylan Pharms. Inc.*, IPR2023-00723, Paper 9, 41 (denying institution based on “Petitioner’s failure to establish a reasonable expectation of success for the changes individually, and in combination”).

The Petition barely gives lip service to reasonable expectation of success and comes nowhere close to establishing it. After citing the legal standard for obviousness, the Petition proceeds to use the word “expectation” only three more times (and only twice in the context of Grounds 1 and 2). (Pet. 56, 99, 116.) And, even in those instances, the Petition simply states in conclusory fashion, and with no analysis, that the prior art would supposedly give a skilled artisan such an expectation. (*Id.*) Petitioner’s expert does no more than parrot the statements in the Petition and similarly offers no analysis of reasonable expectation of success. (EX1002, ¶¶152-154, 225, 312.) The Petition fails for that reason alone. *Eli Lilly and Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021) (affirming

the Board’s finding of non-obviousness based on Petitioner’s failure to establish a reasonable expectation of success even though there was motivation to combine).

Moreover, in the chemistry context, a challenger cannot establish a reasonable expectation of success by merely showing that a chemist could make the claimed compound. *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 555 F. App’x 961, 971 (Fed. Cir. 2014) (where, as here, “drug discovery” is “complicated, unpredictable, and largely conducted through trial and error,” reasonable expectation of success in making a modification can be “precluded... even if [challenger is] able to establish that the prior art taught [the modification]”) (internal quotations omitted).

Instead, the challenger must show that a skilled artisan would reasonably expect the compound to achieve the desired improved properties that motivated the skilled artisan in the first place. *See Daiichi*, 619 F.3d at 1352 (“Proof of obviousness based on structural similarity requires clear and convincing evidence that a medicinal chemist of ordinary skill would have been motivated to select and then to modify a prior art compound (*e.g.*, a lead compound) to arrive at a claimed compound with a reasonable expectation that the new compound would have similar or improved properties compared with the old.”); *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1346 (Fed. Cir. 2013) (“[T]he expectation-of-success analysis must match the highly desired goal, not switch to a different goal that may be a less challenging but also less worthwhile pursuit.”).

Petitioner does not attempt to demonstrate that the skilled artisan would have a reasonable expectation that the proposed modifications would lead to a successful compound, much less a compound with any improved property. As previously discussed, the Petition does not identify any characteristic of orforglipron that a skilled artisan would seek to improve. Nor does the Petition establish that a skilled artisan would reasonably expect the modifications required by the claimed compounds to result in any improved properties.

Petitioner's total failure to show that a skilled artisan would have reasonably expected any improved property to result from making the claimed modifications is an independent reason to deny institution for Grounds 1 and 2. *See, e.g., Mylan Pharms. Inc.*, IPR2023-00723, Paper 9, 30 (denying institution where a POSA would not "have had a reasonable expectation that the [] modification would be beneficial or otherwise 'complement and work synergistically with' [unmodified substituents]"); *Par Pharm.*, IPR2016-00084, Paper 73 at 33-36 (denying institution based on the lack of a reasonable expectation of success).

**V. PETITIONER'S GROUND 3 FAILS BECAUSE IT DEPENDS ON GROUNDS 1 OR 2**

Ground 3 depends on the success of Ground 1 or 2. (Pet. 105-06 ("Compound 65 differs from Compound 19, addressed *supra* in Grounds 1 and 2, by the incorporation of a nitrogen atom into the aromatic ring to which the tetrahydropyran

moiety is attached, as illustrated below. As detailed in Grounds 1 and 2, a POSA would have found it obvious to arrive at Compound 19 based on the combined teachings of Su, Yoshino, Kawai, and Talele.”.) Petitioner cites additional prior art in Ground 3 solely to try to show the incorporation of the nitrogen atom into the aromatic ring of Compound 65 would have been obvious *starting from* Compound 19. (Pet. 106-12.) Thus, if the Office agrees with Ascletis that Petitioner has failed to meet its burden for Grounds 1 and 2, the same is true for Ground 3. *Par Pharm.*, Paper 73 at 36 (“reach[ing] the same conclusion” on second ground because “the second ground of unpatentability . . . obviousness arguments are premised on the conclusion that everolimus would have been obvious” from the first ground).

## **VI. PETITIONER’S GROUND 4 FAILS FOR SIMILAR REASONS TO GROUND 1**

Ground 4 challenges claims 4 and 9, which each depend from claim 1 and require a hemicalcium salt of one or more of the compounds of claim 1. (Pet. 115-16.) Petitioner alleges that claims 4 and 9 are obvious over the combination of Su and Bethel. (*Id.*) Like Ground 1, Petitioner contends that a “POSA would have identified Compound 175 [of Su] as a promising lead compound for further development.” (*Id.*, 115.) Petitioner does not provide any additional reason in Ground 4 that Petitioner would select the Su reference or Compound 175 of Su as a lead compound. (*Id.*, 115-16.) As explained in Section IV.B., Petitioner’s lead

compound analysis for Compound 175 is legally deficient. Ground 4 thus fails for that same reason.

## **VII. GROUNDS 1-4: OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS**

Even if, *arguendo*, Petitioner had met its burden of showing *prima facie* obviousness, Petitioner has not shown it can overcome the objective evidence of non-obviousness, which the Petition does not address. *Stryker Corp. v. KFX Med., LLC*, IPR2019-00817, Paper 10, 28-29 (Sept. 16, 2019) (“We have cautioned petitioners in prior proceedings that petitions may be denied if they do not address known evidence of secondary considerations.”). Here, the challenged patent itself provides evidence of unexpected results that cements non-obviousness.<sup>5</sup>

The challenged patent shows that the claimed compounds have significant biological activity. The patent includes biological activity data for a number of compounds, including all four that Petitioner contends are obvious, Compounds 1, 19, 20, and 65. (EX1001, 199:50-203:67.) That data shows that the claimed compounds have EC<sub>50</sub> values as low as 0.012 nM, much lower than values seen in the prior art. (*Id.*, 201:10.) Moreover, publicly available results from in vitro assays

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<sup>5</sup> In this preliminary response, Ascletis focuses on the unexpected results shown in the challenged patent but reserves the right to present evidence on a range of objective indicia that confirm non-obviousness if the Board institutes trial.

show that one of the claimed compounds, which Ascleitis is developing as ASC30, is 2-3 times more active than orforglipron. (EX2023.) Petitioner cites no evidence to suggest that a skilled artisan would expect the substitutions in the claimed compounds to result in any increase in activity, much less a 2-3-fold difference. *Amgen Inc. v. Sandoz Inc.*, 66 F.4th 952, 963-64 (Fed. Cir. 2023) (finding improved potency not predicted by the prior art sufficient to show unexpected results).

The challenged patent also shows that the claimed compounds have unexpectedly superior pharmacokinetic properties. Table 4 shows the results of a single-dose oral administration PK study comparing Compounds 19, 20, and 65 to orforglipron. (EX1001, 202:37-50.) The results show that, for instance, Compound 19 has an area under the curve (AUC) ***over eight times higher*** than orforglipron. (EX1001, 202:45 (60,043 ng·h/mL for Compound 19), 202:48 (7,222 ng·h/mL for orforglipron).) Compound 19 also had a  $C_{max}$  over five times higher than orforglipron. (EX1001, 202:45 (4,460 ng/mL for Compound 19), 202:48 (799 ng/mL for orforglipron).) Again, Petitioner cites no evidence to suggest that a skilled artisan would expect such a drastic difference between the claimed compounds and orforglipron.

There is also a nexus between the unexpected results and the challenged claims because those claims directly claim the inventive compounds. *In re Albrecht*, 514 F.2d 1389, 1396 (C.C.P.A. 1975) (“That a claimed novel compound possesses

a certain advantageous activity which is not in fact possessed by a prior art compound is itself evidence of the nonobviousness of the subject matter as a whole.”); *Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 536 F.Supp.2d 476, 495-96 (D. Del. 2008) (finding unexpected results where the claimed compound was three times more active and three times less toxic than the prior art compound), *aff’d*, 566 F.3d 989, 997-98 (Fed. Cir. 2009).

Petitioner thus knew of, but failed to overcome, compelling evidence of unexpected results. This constitutes another independent reason for the Board to deny institution on all grounds.

#### **VIII. PETITIONER’S OWN PATENT APPLICATION CEMENTS ITS FAILURE TO ESTABLISH OBVIOUSNESS**

Finally, Petitioner’s own patent application – which it failed to tell the Office about in the Petition – contradicts the obviousness arguments in the Petition.

On December 22, 2023, three months after the earliest priority date for the challenged patent, CSPC filed a Chinese provisional application related to GLP-1 agonists that later published as WO 2025/131,043. (EX2005, 1.) The PCT publication discloses and individually claims Compound 1, one of the compounds that Petitioner now says would have been obvious as of an even earlier priority date. (EX2005, 95-96 (Compound 10 of Claim 10).)

Like claimed compound 1, Compound 10 of the CSPC patent differs from orforglipron in the substitution of a cyclopropyl group for the methyl group on the indazole moiety. (EX1001, 204:5-25; EX1008, 98.) Clearly, before Petitioner found out about Ascletis's earlier patent application, and failed to obtain a license, Petitioner did not think the cyclopropyl for methyl substitution was obvious or it would not have filed a patent application and claimed Compound 10.

The Petition's obviousness arguments, made only after it learned that Ascletis invented and filed first on these compounds, simply cannot be squared with CSPC's patent application. *See Anderson Corp. v. Pella Corp.*, 300 F. App'x 893, 899-900 (Fed. Cir. 2008) (finding that accused infringer's later patent applications to similar subject matter weighed against a finding of obviousness). The Board should not allow Petitioner to do an about face and challenge the very claims it previously represented were patentable.

## IX. CONCLUSION

Petitioner has failed to show it is more likely than not that any claim of the challenged patent is unpatentable, and institution should be denied.

Dated: October 8, 2025

Respectfully submitted,

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**CERTIFICATE OF WORD COUNT (37 C.F.R. § 42.24(d))**

This **Patent Owner's Preliminary Response** complies with the type-volume limitation of 14,000 words, comprising 8,502 words, excluding the parts exempted by 37 C.F.R. § 42.24(a)(1).

This Patent Owner's Preliminary Response complies with the general format requirements of 37 C.F.R. § 42.6(a) and has been prepared using Microsoft® Word 2016 in 14-point Times New Roman font.

Dated: October 8, 2025

By: /Geoffrey D. Biegler/  
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**CERTIFICATION OF SERVICE UNDER 37 C.F.R. §§ 42.6(e), 42.105(a))**

I, Geoffrey D. Biegler, hereby certify that on this 8th day of October 2025,  
the foregoing **PATENT OWNER'S PRELIMINARY RESPONSE** was served  
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