

PGR2025-00057

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

CONJUPRO BIOTHERAPEUTICS, INC.,
Petitioner,

v.

ASCLETIS PHARMA CHINA CO. LTD.,
Patent Owner.

Case No. PGR2025-00057

Patent No. 12,234,236

Title: GLP-1R agonist and therapeutic method thereof

PATENT OWNER'S SUR-REPLY

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TABLE OF ABBREVIATIONS

Abbreviation	Term
Challenged Claims	1-9, 12-17, 21-25
Claimed Compounds	1, 13, 18, 19, 20, 21, 65
Challenged Compounds	1, 19, 20, 65
Su Compounds	Su Compounds 44, 175, and 176
Su 44	Su Compound 44
Su 175	Su Compound 175
Su 176	Su Compound 176
Su 35	Su Compound 35
Yoshino 23	Yoshino Compound 23
Yoshino 40	Yoshino Compound 40
GLP-1R	Glucagon-like Peptide-1 Receptor

**All emphasis added unless otherwise noted

I. INTRODUCTION

Petitioner fails to prove the Challenged Claims are obvious. The Reply, like the Petition, at best shows what a skilled artisan *could* have done in hindsight, not what they *would* have done. That is insufficient under Federal Circuit law.

Petitioner, first, cannot show that a skilled artisan would have selected the Su Compounds as leads. Su discloses no data for those compounds, and Petitioner's substitute evidence – structural analogies to orforglipron, inferences from deuteration, and alleged “SAR” analysis based on different compounds in different references – does not show a skilled artisan would choose the compounds as leads, much less *over* orforglipron. Regardless of the lead, the Reply identifies no credible reason that a skilled artisan would reach the Challenged Compounds; asserting that combining two leads was “the logical next step” is not enough. Moreover, Petitioner barely acknowledges, much less establishes, reasonable expectation of success. Finally, Petitioner fails to rebut unexpected results, offering only the legally incorrect position that substantial differences in degree cannot support patentability.

Unable to support its flawed Petition, Petitioner attempts in Reply to introduce significant new evidence and arguments that the Board should disregard. Regardless, this new evidence is, at best, more of the same, speaking to “could” not “would.”

Because Petitioner has not come close to meeting its burden, the Challenged Claims should be confirmed.

II. PETITIONER HAS FAILED TO PROVE THAT THE CHALLENGED CLAIMS WERE OBVIOUS

A. Ground 1: Petitioner Fails to Show that Compound 19 Was Obvious over Su, Yoshino, Kawai, and Talele

1. Petitioner Has Failed to Show that a Skilled Artisan Would Select Any Su Compound as a Lead

The Su Compounds are not proper “lead compounds.” (Resp., 20-25.) A lead compound is “a compound in the prior art that would be *most promising* to modify,” *Takeda Chem. Indus., Ltd. v. Alphapharm Pty., Ltd.*, 492 F.3d 1350, 1357 (Fed. Cir. 2007), “guided by evidence of the compound’s pertinent properties.” *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1292 (Fed. Cir. 2012).

The “most promising” compound to modify in the prior art was, unquestionably, orforglipron, not the Su Compounds. As the parties agree, at the priority date, orforglipron was a “clinical success,” having demonstrated “full agonist efficacy” and a “favorable safety profile.” (Pet., 1, 10; Reply, 1-3; EX1002, ¶¶48-51.) In contrast, other small molecule GLP-1R agonists had “repeatedly failed,” and “small structural changes” could lead to “unpredictable outcomes,” creating uncertainty for leads other than orforglipron. (Reply, 3.)

Even if they sought a lead other than orforglipron, a skilled artisan would focus on compounds with data suggesting more favorable properties. (EX2079, ¶142; EX1034, 35:18-20.) As Petitioner’s expert conceded, compounds “functionally characterized” with data are more likely leads for further development.¹ (EX2033, 53:20-54:7, 61:1-63:6.) And the prior art disclosed a multitude of orforglipron derivatives, many with data suggesting superior properties to orforglipron, all of which Petitioner ignores in hindsight. (*See, e.g.*, EX2019, Tables 4, 5A, 5B; EX2079, ¶140.)

While ignoring other promising compounds, Petitioner does not show the Su Compounds have *properties* that would cause a skilled artisan to choose one of them as a lead, much less *over* orforglipron. Of its over 200 exemplary compounds, Su discloses activity data for none and pharmacokinetic data for only five, all of which Petitioner contends are irrelevant, raising the question why a skilled artisan would focus on Su at all. (Reply, 4-6; EX1007, 294:29-295:1; EX2079, ¶80.) And, critically, Su does not disclose *any data whatsoever* – activity, pharmacokinetic, or otherwise – for Petitioner’s purported lead compounds. (Resp., 21; Reply, 4.) That

¹ Petitioner downplays its expert’s statements in Reply, but Dr. Pirrung testified in both his declaration and deposition that data was a significant factor in lead selection. (Reply, 5-6; EX1002, ¶¶93-94; EX2033, 61:1-63:6.)

alone makes them improper leads. *Otsuka*, 678 F.3d at 1292 (“In determining whether a chemist would have selected a prior art compound as a lead, the analysis is guided by evidence of the compound’s pertinent properties.”).

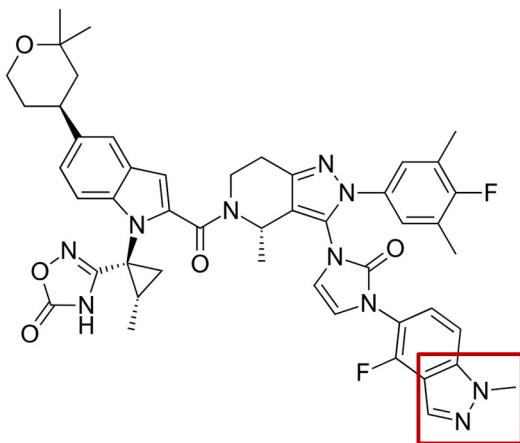
Instead of focusing on properties, Petitioner offers a convoluted path to the Su Compounds based on structural similarity to orforglipron, inferences based on deuteration, and supposed “SAR” analysis in Yoshino. (Reply, 2-15.) Petitioner’s purported evidence does not show that a skilled artisan would choose one of the Su Compounds as a lead over orforglipron.

Orforglipron “core scaffold.” Petitioner is both legally and factually wrong that a skilled artisan – if they considered any lead beside orforglipron – would ignore compounds that did not have the identical “core scaffold.”² (Reply, 2-3.)

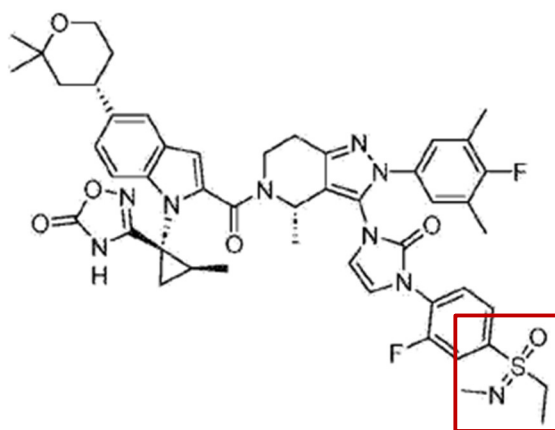
Legally, Petitioner’s argument runs afoul of Federal Circuit law, which requires “the selection of a lead compound [to be] based on its ‘promising useful properties,’ not a hindsight-driven search for *structurally similar* compounds.” *Pfizer Inc. v. Teva Pharms. USA, Inc.*, 555 F. App’x 961, 970 (Fed. Cir. 2014).

² Petitioner contends that compounds have the same “core scaffold” as orforglipron if they have the exact same ring structure. (Reply, 4.) Without agreeing that definition is correct, Ascletis responds with that understanding.

Factually, a skilled artisan would not believe that only compounds with orforglipron's "core scaffold" could have favorable properties because other oral GLP-1 drugs had "failed." (Reply, 2-6.) To the contrary, the prior art includes numerous references that disclose favorable data for compounds *without* orforglipron's "core scaffold." As Petitioner concedes, the only five compounds that Su advanced to biological testing "lack orforglipron's core scaffold." (Reply, 4.) Numerous prior art references disclose exemplary compounds without orforglipron's "core scaffold" that have favorable activity and/or pharmacokinetic data. (*See, e.g.*, EX2019 (Compounds 164, 180, 195, 238); EX2020 (Compounds 102a, 106a, 111a, 118a, 120a, 121a, 124a, 127a, 128a, 129a, 130b, 135a, 138a, 139a, 141a, 142a, 144a, 145a, 146a, 146b, 148a); EX2021 (Compounds 6, 29, 30).) For example, Huang discloses compounds that modify orforglipron's "core scaffold" (by replacing the indazole moiety with phenylsulfoximine) and demonstrate improved activity and pharmacokinetics:



Compound C-5 (Orforglipron)
EC₅₀: 0.033nM
AUC: 4398ng*h/mL (2mpk)
C_{max}: 573ng/mL



Compound 164
EC₅₀: 0.024nM
AUC: 9545 ng*h/mL (5 mpk)
C_{max}: 1793ng/mL

(EX 2019 (annotated), Tables 4, 5A, 5B, [1519].) A skilled artisan would consider all compounds with data if they were searching for a lead different from orforglipron, not only compounds with orforglipron's "core scaffold." (EX2079, ¶¶140-141.)

Contrary to Petitioner's contention, Dr. Wipf did not "caution[] against core scaffold ring changes," (Reply, 3), but instead testified that a skilled artisan would "consider the properties of each different ring moiety" and "test each one to determine how it affects the properties." (EX2079, ¶294.) Likewise, Yoshino does not show that "core scaffold modifications are associated with decreased activity," a contention that lacks any expert support. (Reply, 3.) Instead, Petitioner cherry-picks two Yoshino compounds (4 and 57) without the "core scaffold" that have a

lower EC₅₀, while ignoring numerous Yoshino examples with *improved* activity. (See, e.g., EX1008, Compounds 11 (1.1nM), 32 (0.94nM), 39 (1.0nM).) Petitioner’s “core scaffold” argument is also contradicted by Ground 3, where Petitioner argues that changing the “core scaffold” of orforglipron was a “rational and routine medicinal chemistry strategy.” (Pet., 4; EX1002, ¶¶268-287.) Petitioner’s “core scaffold” argument is improper hindsight based on structural similarity to the Challenged Compounds.

Deuteration. Petitioner is also wrong that a skilled artisan would focus on the Su Compounds because they are *deuterated*. Again, if searching for a lead besides orforglipron, a skilled artisan would follow the data, not suppositions about Su’s motivation for deuterating a compound. (Resp., 23; EX2079, ¶¶144-145.)

Petitioner for the first time argues that a skilled artisan would know a deuterated compound must have “good activity.” (Reply, 6.) But the cited portions of Dr. Pirrung’s declaration say no such thing. (See EX1002, ¶¶150-154.) And even if it were right, Petitioner does not explain why a skilled person would choose compounds with unspecified “good activity” over clinically validated orforglipron.

Petitioner also incorrectly argues that a skilled artisan would focus on the Su Compounds because deuteration suggests they had “already been characterized” for “pharmacokinetic properties.” (Reply, 6-7.) Even if true, a skilled artisan would not

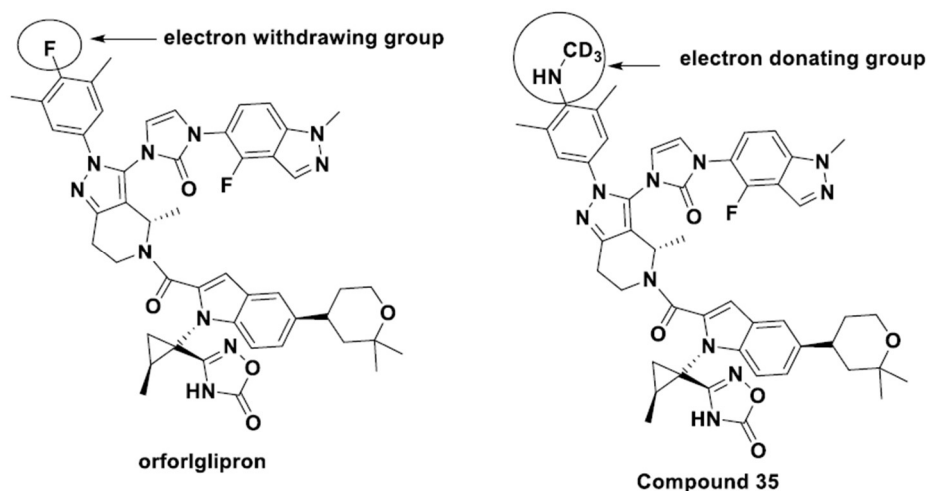
know those properties because Su does not provide that data. (EX1007, 294:29-295:1.) If anything, a skilled artisan would suspect the Su Compounds had a pharmacokinetic liability that deuteration did not fix. (EX2079, ¶145.)

Petitioner is also wrong that deuteration to “expand intellectual property” is relevant to lead compound selection. (Reply, 7.) Petitioner’s cited evidence merely speaks to potential reasons to deuterate a compound generally, not lead compound selection. (EX1036, Table 1.) And Dr. Wipf did not equate IP expansion with lead compound analysis but said deuteration might “broaden the intellectual property protection” *if* the deuterated compound showed “utility or the unexpected results.” (EX1034, 182:20-183:8.) A skilled artisan would not choose a lead compound based on another’s attempt to expand IP protection, particularly without supporting data. (EX2079, ¶145; EX1034, 276:15-278:11.)

Additional Steps to the Su Compounds. Even incorrectly eliminating Su’s compounds without the “core scaffold” and then focusing only on the remaining compounds that are deuterated (while, simultaneously, ignoring Su’s only compounds with any data) *still* does not result in Petitioner’s leads.

Su 35 also has orforglipron’s “core scaffold” and is “deuterated,” but Petitioner summarily dismisses it in yet another act of hindsight. (Reply, 8.) Petitioner’s contention that Su 35 would have “less favorable” characteristics is pure

speculation because Su provides no data for the compound. (Reply, 8.) Moreover, Petitioner strangely argues that a skilled artisan would discard Su 35 because Dr. Wipf supposedly “cautioned that ring changes could significantly alter compound properties through electrostatic interactions,” (Reply, 8), but Su 35 does not have a “ring change,” as shown below:



(*Id.*) Petitioner’s disposal of Su 35 is just more hindsight.

Petitioner also provides no explanation why a skilled artisan would select *undeuterated* Su 175 as a lead if they focused on Su 176 *because it was deuterated*. Petitioner alleges, with no support, that “[a] POSA would have understood that the *nondeuterated* parent compounds corresponding to deuterated [Su] compounds 44 and 176 were of particular interest, having been selected for deuteration from among hundreds of compounds disclosed in Su and Yoshino.” (Reply, 15.) But that

argument makes little sense: if a skilled artisan deuterated a compound to, for instance, try to improve pharmacokinetics, why would they abandon the deuterated compound, particularly in the absence of data? Petitioner provides no answer.

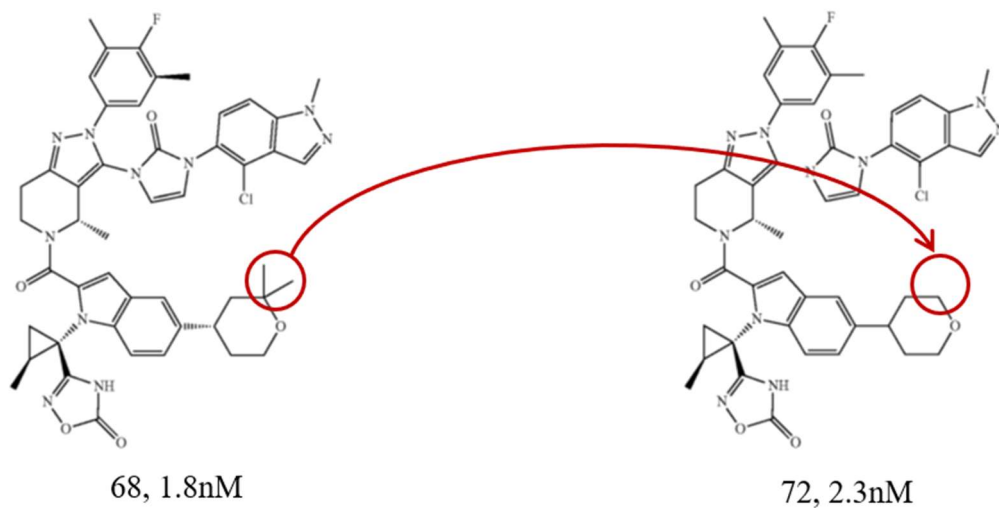
Yoshino 23 and Supposed “SAR.” In addition to its “core scaffold” and deuteration arguments, Petitioner makes a series of brand-new arguments, found nowhere in the Petition, based on Yoshino. The Board should not consider these belated arguments, but regardless, they do not show a skilled artisan would select any Su Compound as the lead.

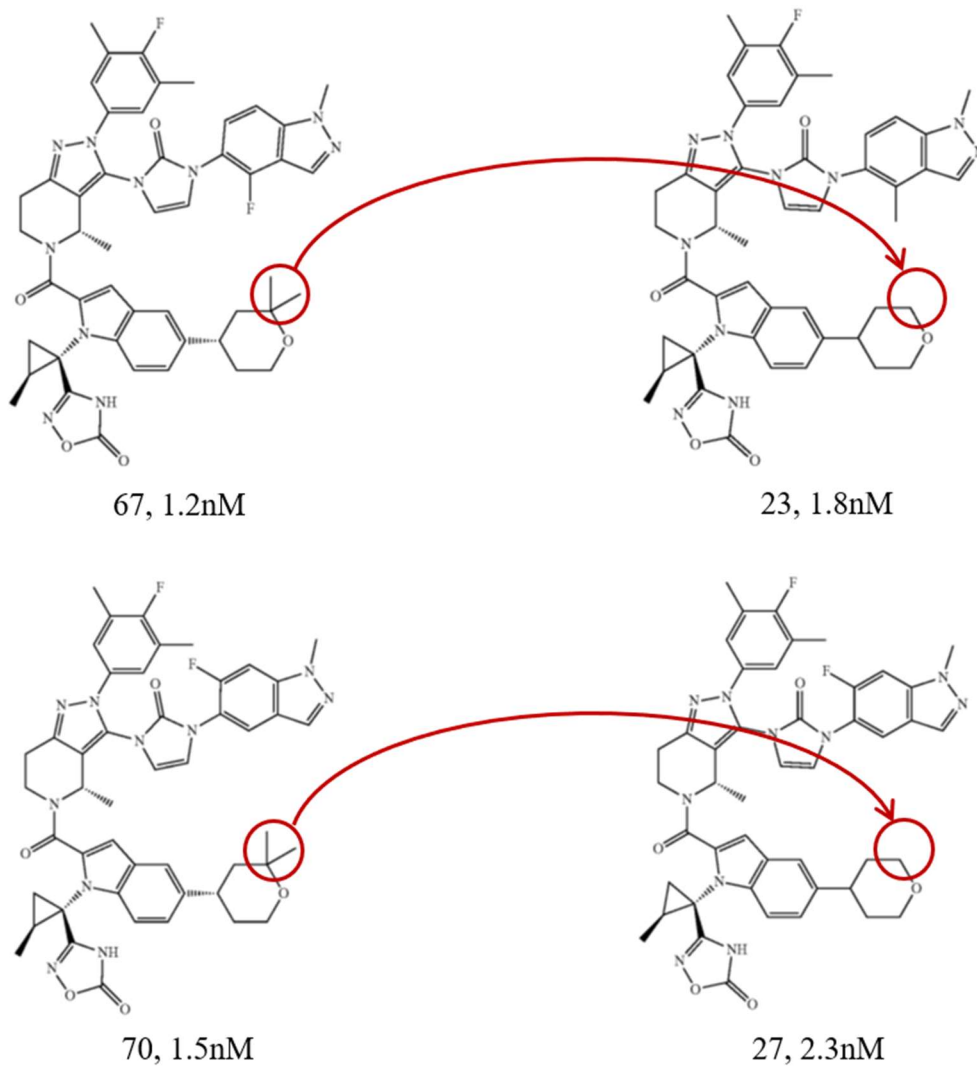
Yoshino 23 does not give a skilled artisan a reason to select Su 44 as a lead. (Reply, 7-9.) Initially, Petitioner did not identify Yoshino 23 as prior art or even mention it in the Petition, and the Board should disregard Petitioner’s new arguments based on it. Consolidated Trial Practice Guide, 73 (Nov. 21, 2019); *see also Wasica Finance GMBH v. Cont’l Auto. Sys.*, 853 F.3d 1272, 1286 (Fed. Cir. 2017).

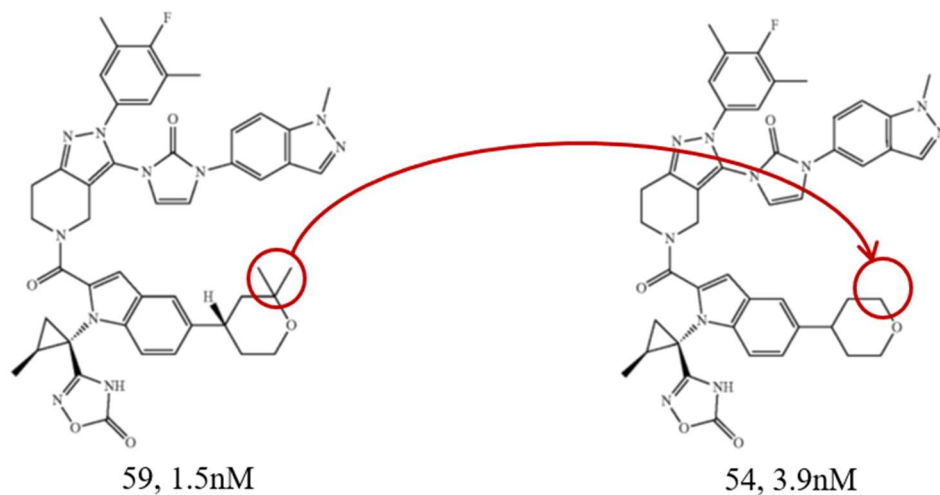
Regardless, Petitioner ignores that Yoshino 23 has a *worse* EC_{50} than orforglipron, pointing a skilled artisan away from its unsubstituted THP ring. (EX1008, 310:40-311:50, *compare* Yoshino 67 (i.e., orforglipron) (1.2nM) *with* Yoshino 23 (1.8nM).) Yoshino 23 also has a worse EC_{50} than at least 26 other Yoshino compounds, which Petitioner bypasses in more hindsight. (*See id.* (Compounds 11, 16-19, 21, 26, 29-33, 38-39, 43-45, 59, 61-63, 66-67, 70-71, 77).)

Yoshino also does not disclose an “SAR” showing removal of the dimethyl group on the THP ring (as in Su 44) is “beneficial for activity.” (Reply, 9-10.) Initially, the Board should disregard Petitioner’s new “SAR” argument, which is found nowhere in the Petition, relies on Yoshino compounds not previously raised, and lacks any expert support. Consolidated Trial Practice Guide, 73 (Nov. 21, 2019). Nonetheless, Yoshino does not disclose an SAR: it provides EC₅₀ data for numerous compounds but does not draw any conclusions about the relationship between structural features and activity like an SAR would. (*Compare* EX1008, 310:40-311:50 *with* EX2040, EX2087.) In fact, Petitioner ignores numerous examples in Yoshino showing a **decrease** in activity for compounds without the dimethyl group.

Dimethyl removal decreases activity (Compound, EC₅₀)







(EX1008, 310:40-311:50.) Yoshino’s compounds with an unsubstituted THF in no way support Su 44 as a lead.

Similarly, Yoshino does not include an “SAR” showing that replacing the methyl group on the indazole moiety with a THF ring (as in Su 175/176) “improves” or “maintains” activity. (Reply, 11-13.) Petitioner’s SAR argument is, again, brand new and without any expert support. (*Id.*) Regardless, as explained in Response, if anything, Yoshino shows that orforglipron-derivatives with a THF ring on the indazole moiety **decreased** activity. (Resp., 30-31.) Indeed, Yoshino 40, which has the same structure as orforglipron but replaces the methyl group on the indazole moiety with a THF ring, has a nearly two-fold **decrease** in activity, which Dr. Pirrung conceded was “significant.” (EX1008, 310:40-311:50; EX2079, ¶76; EX2033, 65:16-66:6; Resp., 30-31.) Moreover, Petitioner has no response to Ascleitis’s

evidence that one cannot extrapolate results from THF rings to cycloalkyl groups because they have different properties and effects as substituents. (Resp., 32.)

“Structural Data.” Finally, Petitioner’s “structural data” does not support Su 175/176 as leads. (Reply, 11.) Kawai merely provides the structure of orforglipron bound to the GLP-1 receptor and says nothing about potential substitutions or Su. (EX2079, ¶83, EX1004, 1-2, 8.) Dr. Fan’s “docking analysis,” in addition to being belated evidence that the Board should not consider, as explained below, merely asserts that a cyclopropyl ring “can” be accommodated by the relevant binding pocket. (Reply, 11; EX1035, ¶¶35, 37.) Whether the binding pocket “can” accommodate a cyclopropyl is not in question. Instead, the relevant question is whether a skilled artisan “would have been motivated” to select Su 175/176 as a lead over orforglipron, *InTouch Techs., Inc. v. VGO Commc’ns, Inc.*, 751 F.3d 1327, 1352 (Fed. Cir. 2014), something Dr. Fan’s declaration does not address.

2. Petitioner Has Not Established a Motivation to Modify the Su Compounds to Achieve Compound 19

The Petition did not identify any reason that a skilled artisan would have modified the Su Compounds to arrive at Compound 19. (Resp., 25-28.) In Reply, Petitioner adds little, making generic arguments that “[t]he continuing need to modify known drug candidates with good pharmaceutical profiles is well-recognized

by a POSA” and that combining Petitioner’s lead compounds would be “the logical next step.” (Reply, 2, 17-18.) The Federal Circuit has repeatedly rejected such conclusory motivations. *Arendi S.A.R.L. v. Apple Inc.*, 832 F.3d 1355, 1362 (Fed. Cir. 2016) (“[O]ur cases repeatedly warn that references to ‘common sense’—whether to supply a motivation to combine or a missing limitation—cannot be used as a wholesale substitute for reasoned analysis.”); *see also Takeda Pharm. Co. v. Torrent Pharms. Ltd.*, 844 F. App’x 339, 342 (Fed. Cir. 2021). The remainder of Petitioner’s arguments speak to whether “one of ordinary skill in the art could combine” teachings, not whether “they would have been motivated to do so,” *InTouch Techs.*, 751 F.3d at 1352, and should be rejected.

Starting with Su 44. Petitioner has failed to show that a skilled artisan would replace the methyl on Su 44’s indazole with a cyclopropyl *and* remove both deuteriums from the THP moiety. As previously explained, and uncontested in Reply, a skilled artisan could modify Su 44 at many positions, had many options at each position, and would not initially replace methyl groups because of their outsized impact. (Resp., 17, 29; EX2079 ¶52; EX2028, Abstract.)

Yoshino does not provide the required motivation and, in fact, teaches away from using a cycloalkyl on the indazole moiety. Petitioner repeats that Yoshino’s THF-substituted compounds encourage the use of a “ring structure” but ignores that

many THF-substitutions in Yoshino result in lower activity. Regardless, a skilled artisan would not draw conclusions about cycloalkyl substitutions based on THF rings. (Resp., 30-32.) Petitioner also argues Yoshino does not teach away because it is “entirely silent” on cycloalkyls, (Reply, 16), but provides no counterevidence to Dr. Wipf’s testimony that a skilled artisan would understand Yoshino to purposefully exclude cycloalkyls given the large number of options it provides for the indazole moiety and its express inclusion of cycloalkyls at many other positions. *See Arctic Cat Inc. v. Bombardier Recreational Products Inc.*, 876 F.3d 1350, 1360 (Fed. Cir. 2017) (“[P]rior art need not explicitly ‘teach away’ to be relevant to the obviousness determination”).

Kawai also does not provide the required motivation. Petitioner does not contest Kawai’s silence on modifying orforglipron. (Resp., 32-33.) And, as shown by Dr. Wipf, Kawai does not show that the GLP-1R binding pocket for the indazole was “spacious and hydrophobic” as the Petition contended. (EX2079, ¶¶170-179.)

Faced with Dr. Wipf’s testimony, and Dr. Pirrung’s lack of experience with cryo-EM structures like in Kawai, (EX2033, 34:9-36:16), Petitioner submits a Reply declaration from brand-new expert, Dr. Fan. (EX1035.) That declaration could have and should have been submitted with the Petition, and the Board should not consider

it. Consolidated Trial Practice Guide, 73 (Nov. 21, 2019); *Intelligent Bio-Systems, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369–70 (Fed. Cir. 2016).

Improper timing aside, Dr. Fan is not a person of ordinary skill in the art, (Pet., 44; Resp., 16), and does not attempt to show what a skilled artisan would have known or done at the priority date. **First**, Dr. Fan provides a “docking analysis,” found nowhere in the prior art, that concludes only that GLP-1R “can accommodate” a cyclopropyl group on the indazole moiety. (EX1035, ¶¶35, 37.) Dr. Fan conceded at deposition that she “didn’t pick the[] compounds” to evaluate in her docking analysis but was “asked to evaluate [them]” by counsel, evidencing hindsight, not that a skilled artisan would have performed these analyses. (EX2089, 95:22-23.) Moreover, Dr. Fan admitted her “docking analysis” does not predict activity or pharmacokinetics and, even if it could, merely showed that a cyclopropyl has a “comparable” docking score to numerous other substituents, including methyl. (EX2089, 134:21-135:14, 138:24-141:17; EX1035, ¶34). **Second**, Dr. Fan’s “physicochemical character” analysis of the indazole binding pocket relies on brand-new cryo-EM structures and merely concludes that *part* of the GLP-1R pocket that binds to indazole is hydrophobic. (EX1035, ¶41; Reply, 21-22.) Indeed, Dr. Fan agreed with Dr. Wipf’s calculations showing that the closest amino acid residue to the indazole methyl is polar and thus hydrophilic, contradicting her own

characterization, and favoring polar, hydrophilic substituents unlike cycloalkyls. (EX2089, 156:24-158:19; EX2079, ¶95.) Dr. Fan's analysis does not show that a skilled artisan would have replaced methyl with cyclopropyl at the priority date.

Talele also does not provide the required motivation. Petitioner has no response to Talele's examples where cyclopropyl substitutions led to *worse* properties and its statements cautioning the use of cyclopropyl substituents as "context dependent." (Resp., 38; EX1009, 20.)

Finally, Petitioner is also wrong that a skilled artisan would replace the methyl on the indazole moiety with cyclopropyl because cyclopropyl groups are supposedly "most comparable" to methyl groups. (Reply, 23, 30-31.) As Dr. Wipf explained, methyl and cyclopropyl groups in fact have many differences that can lead to different results. (EX2079, ¶¶50-56, 172, 187.) But even assuming some similarities, Petitioner does not explain why they would motivate a skilled artisan to replace the indazole methyl with cyclopropyl. Instead, a skilled artisan would make changes to try to improve, not maintain, properties. (EX2079, ¶¶48, 153.)

As to the deuteriums on Su 44, Petitioner provides no reason why a skilled artisan would remove them to achieve Compound 19.

Starting with Su 175. Petitioner also does not show that a skilled artisan would modify Su 175/176 to remove the dimethyl group from the THP moiety and,

for Su 176, remove both deuteriums. Petitioner does not contest Ascletis's evidence that a skilled artisan could attempt to modify Su 175/176 at many different positions other than the THP moiety with many options at each potential position. (Resp., 17.)

Among all those options, Petitioner does not show motivation to remove the dimethyl group from the THP moiety. Su's limited data is unrelated to removing the dimethyl group from the THP moiety. (EX1007, 294:29-295:1.) And, as discussed above, Yoshino discloses multiple examples where removing the dimethyl group lowered activity, including a direct comparison between orforglipron and Yoshino 23. (EX1008, 310:40-311:50.) Moreover, despite experimentation with an unsubstituted THP moiety, Yoshino moved forward with orforglipron, which includes the dimethyl group. (EX1008, 311:51-313:34.) Petitioner does not substantively respond to any of these points.

Petitioner further has not explained why a skilled artisan would remove the deuteriums from Su 176.

Obvious-to-try. Without any evidence of motivation, Petitioner pivots to an obvious-to-try theory, citing *KSR* for the proposition that “[w]here a skilled artisan pursues ‘known options’ from a ‘finite number of identified, predictable solutions,’ obviousness is appropriate.” (Reply, 16.) Petitioner does not cite a single case

finding a new chemical compound unpatentable as obvious-to-try. Regardless, the options here were neither “finite” nor “predictable.”

Petitioner fails to show a “finite” number of potential solutions for developing an oral GLP-1 agonist. Indeed, the prior art discloses thousands of exemplary orforglipron-derivative compounds and generic formulas that provide endless design choices. (Resp., 49.) A skilled artisan could have modified numerous positions on orforglipron and had thousands of possible options for each position. (*Id.*)

Petitioner does not dispute the vast number of choices in the prior art but tries to improperly narrow them by (1) excluding options for “core scaffolds substantially different from orforglipron” or provided by “broad genera” and (2) focusing only on the options in its asserted references. (Reply, 18-19.) But the question is whether *the prior art as a whole* provides a finite number of solutions, not just some subset of the prior art cherry-picked by Petitioner. *Ortho–McNeil Pharm., Inc. v. Mylan Labs., Inc.*, 520 F.3d 1358, 1364 (Fed. Cir. 2008) (the number of options must be “finite, and in the context of the art, small or easily traversed.”). In reality, a skilled artisan also would not so limit themselves, (EX2079, ¶¶140-141), but even incorrectly focusing on Petitioner’s prior art, Su and Yoshino alone provide countless ways to try to modify orforglipron. (EX2079, ¶216-17; EX1007, 5:1-7:4; EX1008, 3:1-6:2.)

Petitioner also does not show the potential solutions were predictable. Instead, Petitioner admits that “small changes in molecular structure can have unpredictable effects on properties such as biological activity and toxicity” and that other small molecule GLP-1R agonists had “repeatedly failed.” (Reply, 3.) Ascletis’s evidence likewise supports that small structural changes to orforglipron can result in unpredictable differences in properties. (Resp., 50-53.)

3. Petitioner Fails to Establish Reasonable Expectation of Success

The Petition failed to articulate any goal that a skilled artisan would seek, much less reasonably expect, to achieve in modifying orforglipron. (Resp., 50.) In Reply, Petitioner summarily states “[t]he combined effects of cyclopropyl incorporation and methyl removal would have been reasonably expected to provide an active compound.” (Reply, 18.) But a skilled artisan would not pursue a new compound simply because it might be “active.” (EX2079, ¶¶48, 153.) Even so, Petitioner does not cite any expert testimony supporting that a skilled artisan would expect Compound 19 to be “active.” Instead, Petitioner merely recycles the same unsupported arguments about Yoshino’s supposed “SAR,” which are wrong for the reasons discussed above. (*See* §II.A.1; Reply, 24-27.)

4. Petitioner Has Failed to Rebut Substantial Evidence of Objective Indicia

Unexpected Results. Compound 19 has *7-fold* higher potency and *3-4 fold* better pharmacokinetics than Su 175 and a *3-fold higher* potency and up to *43-fold* better pharmacokinetics than orforglipron. (Resp., 54-56.) Petitioner’s expert conceded these differences are “significant.” (EX2033, 65:22-66:6.)

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

Petitioner does not contest that these improvements are significant but, instead, incorrectly argues that they are legally insufficient. While a “mere difference in degree” cannot render a compound non-obvious, a “marked superiority” in an expected property can. *Bristol-Myers Squibb Co. v. Teva Pharms. USA, Inc.*, 752 F.3d 967, 977 (Fed. Cir. 2014); *see also In re Hoch*, 428 F.2d 1341, 1344 n.5 (CCPA 1970) (explaining that unexpected “differences in properties” can mean “significant difference in degree of the same property” amounting to a “marked superiority” when evaluating unexpected results.) The Federal Circuit has

previously found similar differences in properties to support unexpected results.

Amgen Inc. v. Sandoz Inc., 66 F.4th 952, 963-964 (Fed. Cir. 2023).

[REDACTED]
[REDACTED]
[REDACTED] Petitioner
has no response to this difference in kind. (Reply, 35-36.)

Petitioner is wrong that the improvements in activity and pharmacokinetics were expected. (Reply, 35.) A skilled artisan would not have expected Compound 19's significant improvement in activity "based on Yoshino's SAR demonstrating the beneficial effects of unsubstituted THP." (Reply, 35.) As explained previously, Yoshino does not provide an SAR analysis, and its unsubstituted THP examples show mixed results and nothing close to the significant improvements in activity demonstrated by Compound 19. (§II.A.1.)

Nor would a skilled artisan have expected Compound 19's improved pharmacokinetic properties based on "well known effects of cyclopropyl substitution in enhancing metabolic stability and extending half-life." (Reply, 36.) Petitioner's only evidence on this point is Talele, which has nothing to do with the claimed GLP-1R agonists and itself says cyclopropyl substitution effects are "context dependent." (Reply, 36 (citing EX1009, 24); EX2079, ¶113.)

Failure of Others. Petitioner agrees that other oral GLP-1 drugs have failed, (Reply, 37), but incorrectly dismisses these failures because they do not have “meaningful structural similarity with the orforglipron scaffold.” (Reply, 37.) Petitioner provides no explanation why the failure of other oral GLP-1 candidates, which sought to solve the same problem, should not be considered. *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1285 (Fed. Cir. 2000) (“[W]hen evidence in the record fully supports a finding that others in the industry failed to solve the problem, then objective considerations ‘may . . . establish that an invention appearing to have been obvious in light of the prior art was not.’”).

Petitioner also incorrectly argues that “[t]here is no evidence the challenged compounds, as derivatives of the clinically successful orforglipron, address any additional hepatotoxicity concerns.” (Reply, 37.) [REDACTED]

[REDACTED]

[REDACTED]

B. Ground 2: Petitioner Fails to Show Compounds 1, 19, and 20 Are Obvious over Yoshino, Kawai, and Talele

1. Petitioner Fails to Establish Motivation to Make the Changes to Orforglipron Required to Achieve Compounds 1, 19 or 20

Compound 1. Petitioner has not shown that a skilled artisan would be motivated to replace the methyl group on the indazole moiety of orforglipron with a

cyclopropyl. Petitioner mainly repeats its incorrect arguments based on Yoshino, Kawai, and Talele from Ground 1. (Reply, 23-24.) As explained above in Section II.A.1-2, those references do not provide the required motivation and, in fact, teach away from the use of cycloalkyls on the indazole moiety. Likewise, Dr. Fan's untimely declaration, which should not be considered, says nothing about what a skilled artisan *would* have done at the priority date. (§II.A.2.)

Compound 19. Petitioner has not shown that a skilled artisan would be motivated to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl *and* remove the dimethyl group on the THP moiety.

In Reply, Petitioner relies heavily on Su, which Petitioner did not assert in Ground 2, (Pet., §XIII.B), and Yoshino 23, which was never raised in the Petition. (Reply, 25-27.) The Board should disregard Petitioner's arguments based on either.

Petitioner's Ground 2 arguments for Compound 19, otherwise, largely mirror its Ground 1 arguments. Petitioner does not show that a skilled artisan would have been motivated to modify orforglipron to replace the methyl group on the indazole moiety *or* remove the dimethyl group on the THP moiety for the reasons previously discussed. (*Supra* Compound 1; §II.A.1-2; Resp., §V.A.) Moreover, Petitioner still has not articulated a reason that a skilled artisan would make *both* required changes.

Compound 20. Petitioner has not shown that a skilled artisan would be motivated to modify orforglipron to replace the methyl group on the indazole moiety with a cyclobutyl *and* remove the dimethyl group on the THP moiety. Petitioner’s Reply on Compound 20 spans less than half a page and does not meaningfully respond to Ascleitis’s Response. (Reply, 27.) Moreover, Petitioner again improperly relies on Su, which is not cited in the Petition as part of Ground 2, and should not be considered for Compound 20. (Pet., §XIII.B.)

2. Petitioner Fails to Address Reasonable Expectation of Success

Petitioner says almost nothing about reasonable expectation of success for Ground 2, including one conclusory sentence that the Challenged Compounds would have been reasonably expected to have improved activity and PK properties. (Reply, 26-27.) For all the reasons discussed in Ground 1 and in the Response, Petitioner has failed to support that claim. (§II.A.2.a; Resp., 63-65.)

3. Petitioner Does Not Rebut the Significant Objective Indicia

As explained above, unexpected results and failure of others confirm that Compound 19 was not obvious. (§II.A.4.) Compounds 1 and 20 likewise have “significant” improvements in potency and/or pharmacokinetics compared to the closest prior art. (Resp., 65-67; EX2033, 56:4-14.) Petitioner claims that those significantly improved properties are legally insufficient, but a “marked superiority”

in a property, as seen with the Challenged Compounds, supports non-obviousness. *Bristol-Myers Squibb*, 752 F.3d at 977. Moreover, for the reasons discussed above, failure of others supports non-obviousness of Compounds 1 and 20. (§II.A.4.)

C. Ground 3: Petitioner Fails to Show Compound 65 Is Obvious

Petitioner's Reply barely addresses Ground 3 or Ascletis's evidence on Compound 65's non-obviousness. (Reply, 31-33; Resp., §V.C.) Indeed, Petitioner's only response rests on the factually and legally flawed proposition that *Meng* "discloses only two specific options to modify orforglipron" and therefore a "finite number of identified, predictable solutions" were available in the prior art. (Reply, 32.) As previously explained, the relevant question under *KSR* is whether there were a finite number of solutions available in the prior art *as a whole*, not just the particular references Petitioner cherry-picked. *Ortho-McNeil Pharm.*, 520 F.3d at 1364. As Dr. Wipf explained, and Petitioner has not rebutted, the prior art disclosed nearly infinite options for modification of orforglipron, even just focusing on potential nitrogen ring substitutions. (EX2079, ¶278.)

Petitioner also fails to rebut Ascletis's evidence that Compound 65 demonstrates unexpectedly superior properties to both orforglipron and Su 175. Petitioner is wrong that Compound 65's significant improvements in pharmacokinetic properties and solubility compared to the closest prior art are

legally insufficient to support patentability. *Bristol-Myers Squibb*, 752 F.3d at 977. Moreover, Petitioner does not cite any evidence that a skilled artisan would expect a nitrogen substitution to improve solubility by anything close to the 100-fold improvement demonstrated by Compound 65. (Reply, 36; EX2081, EX2079, ¶324.)

D. Grounds 1-3: Petitioner Fails to Address Claims 2-4, 8-9, 13-14, 16-17, and 22-23

Petitioner does not reply to Ascleitis’s evidence that a skilled artisan would not have been motivated to make the salts in Claims 2-4, 8-9, 13-14, 16-17, and 22-23 or have a reasonable expectation of success. (Resp., 82-83.) For that reason, and those in the Response, Petitioner has failed to meet its burden on those claims.

E. Ground 4: Petitioner Fails to Show that the Hemicalcium Salt of Compound 1 Is Obvious

Petitioner also has failed to show that Claims 4 and 9 are obvious over Su and Bethel. As explained above, a skilled artisan would have no reason to select Su 175 as a lead compound. (§II.A.1.) Moreover, a skilled artisan would not have been motivated to make a hemicalcium salt of Su 175, nor have a reasonable expectation of success, given the undisputed unpredictability of salt formation. (Resp., 85-86.)

Petitioner argues that courts have “consistently” found salt forms of known active ingredients obvious, based solely on *Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348 (Fed. Cir. 2007). (Reply, 33.) But *Pfizer* is inapposite because the evidence there

showed that a skilled artisan would have narrowed the possible salts to only a few, 480 F.3d at 1366, something Petitioner does not attempt to show here. In other cases, the Federal Circuit has made clear that the patentability of salt forms depends on the particular facts of each case. *Sanofi–Synthelabo v. Apotex, Inc.*, 470 F.3d 1368, 1379 (Fed. Cir. 2006).

Petitioner also incorrectly argues that a skilled artisan would have had a reasonable expectation that Compound 1 would form a hemicalcium salt because it has the same “acidic proton” as orforglipron. (Reply, 33.) But Petitioner reaches that conclusion without any support; the portion of Dr. Pirrung’s declaration Petitioner cites does not say anything about the position of a proton in the compounds. (*See* EX1002, ¶¶307–312.) Moreover, Dr. Pirrung admitted that he has never been involved in the discovery of salts, (EX2033, 19:14-25:18), and his testimony should be given no weight on this issue.

III. CONCLUSION

For the reasons set forth above and in Ascleitis’s Response, Petitioner has failed to meet its burden to establish unpatentability of any Challenged Claim.

Dated: July 9, 2026

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(c), the undersigned certifies that the foregoing Patent Owner's Sur-Reply contains, as measured by the word-processing system used to prepare this paper, 5,580 words. This word count does not include the items excluded by 37 C.F.R. § 42.24 as not counting toward the word limit.

Dated: July 9, 2026

By: /Geoffrey D. Biegler/
Geoffrey D. Biegler
Admitted *pro hac vice*

CERTIFICATION OF SERVICE UNDER 37 C.F.R. §§ 42.6(e), 42.205(a)

I, Geoffrey D. Biegler, hereby certify that on this 9th day of July, 2026, the foregoing **PATENT OWNER'S SUR-REPLY** was served electronically via email on the following:

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