

Case No. PGR2025-00057

Patent No. 12,234,236

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 RESPONSE

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TABLE OF ABBREVIATIONS

Abbreviation	Term
Claimed Compounds	1, 13, 18, 19, 20, 21, 65
Challenged Claims	1-9, 12-17, 21-25
Challenged Compounds	1, 19, 20, 65
GLP-1R	Glucagon-like Peptide-1 Receptor
Cryo-EM Structure:	Cryo-electron microscopy Structure
TCP	Target Compound Profile
TPP	Target Product Profile

I. INTRODUCTION

The Petition is no more than a post-hoc analysis of how a skilled artisan *could have* arrived at the Challenged Compounds with the Challenged Patent in hand. Petitioner and its expert, Dr. Pirrung, base their argument on 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 asserts the well-known drug orforglipron, as first disclosed in Yoshino, as a primary reference against all the Challenged Compounds. But Petitioner fails to identify a single shortcoming of orforglipron or a problem to solve, much less one that would motivate a skilled artisan to make the changes needed to arrive at the Challenged Compounds. Indeed, far from suggesting the required changes, Yoshino teaches away from the change required in all the claimed compounds and rejects a second relevant change in favor of orforglipron.

Petitioner plucks Su, its other primary reference against Challenged Compound 19, out of a sea of prior art on orforglipron derivatives based solely on hindsight. Even worse, Petitioner focuses on two compounds (44 and 175) for

which Su discloses no data whatsoever, while completely ignoring five other compounds that Su advanced to pharmacokinetic studies, indicating their lead status. No skilled artisan would focus on Su's Compounds 44 and 175, and Dr. Pirrung's convoluted rationale for doing so could only result from the use of hindsight. Moreover, even starting with one of Su's compounds, Petitioner fails to establish a motivation to make their respective modifications in a single compound.

The Petition similarly comes up short on reasonable expectation of success, including only two conclusory sentences on that issue. In fact, nothing in the prior art would make a skilled artisan reasonably expect success with the Challenged Compounds. Quite the opposite, the evidence shows that even small changes to orforglipron can result in wildly different properties, from significant improvement to the complete loss of activity, with no way to predict the outcome in advance.

The objective evidence cements non-obviousness. After multiple failures from major companies pursuing small molecule GLP-1R agonists, the Challenged Compounds demonstrate superior, unexpected properties, and one of them is showing great promise in clinical trials. For instance, Challenged Compound 19 demonstrated a more than ***3-fold improvement*** in potency (EC₅₀) and a ***43-fold improvement*** in total drug exposure (AUC) compared to orforglipron. Even Dr. Pirrung was forced to admit at deposition that improvements of that magnitude are “significant[]” in the GLP-1R agonist context. (EX2033, 55:15-56:14.)

At bottom, Petitioner fails to establish multiple elements required for obviousness and cannot show by a preponderance of the evidence that any of the Challenged Claims are obvious. The Challenged Claims should be maintained.

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.*; EX2079, ¶61.)

Over the last decade, glucagon-like peptide-1 receptor agonists have changed the treatment paradigm for obesity. (EX2016, 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.*, 2-3; EX2079, ¶62.)

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.*, 2, 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; EX2079, ¶¶63-64.)

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 EC₅₀ 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,

compared to the once-weekly subcutaneous injections then required for peptide GLP-1R agonists. (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); EX2079, ¶66.) Neither Petitioner, nor its expert Dr. Pirrung, point to any shortcoming of orforglipron that skilled artisans in the field were seeking to improve as of the priority date of the Challenged Patent.

By 2023, Phase 2 clinical trials showed that daily oral orforglipron caused weight reduction and related benefits similar to that observed with the injectable peptide 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 Phase 3 trial showed that once-daily orforglipron resulted in similar weight reduction and safety profile as that observed with injectable peptide GLP-1R agonists, such as semaglutide and tirzepatide. (EX2083, 6.)

B. The '236 Patent Discloses and Claims Novel GLP-1R Agonists with Unexpectedly Superior 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.) The '236 Patent discloses and claims those superior compounds. (EX2079, ¶123)

The '236 Patent is directed to “compounds that bind to and act as agonists or modulators of the glucagon-like peptide-1 receptor (GLP-1R)” and the use of such compounds for the treatment of GLP-1R-mediated diseases and conditions. (EX1001, 1:49-55.) It discloses over 60 novel compounds with a similar core structure to orforglipron but with one or more modifications, some of which result in unexpectedly superior properties. (EX1001, 167:38-200:48; EX2079, ¶121)

Each of the Challenged Claims covers one or more of seven of the disclosed compounds: Compounds 1, 13, 18, 19, 20, 21 and 65. (EX1001, 204:10-220:58.)

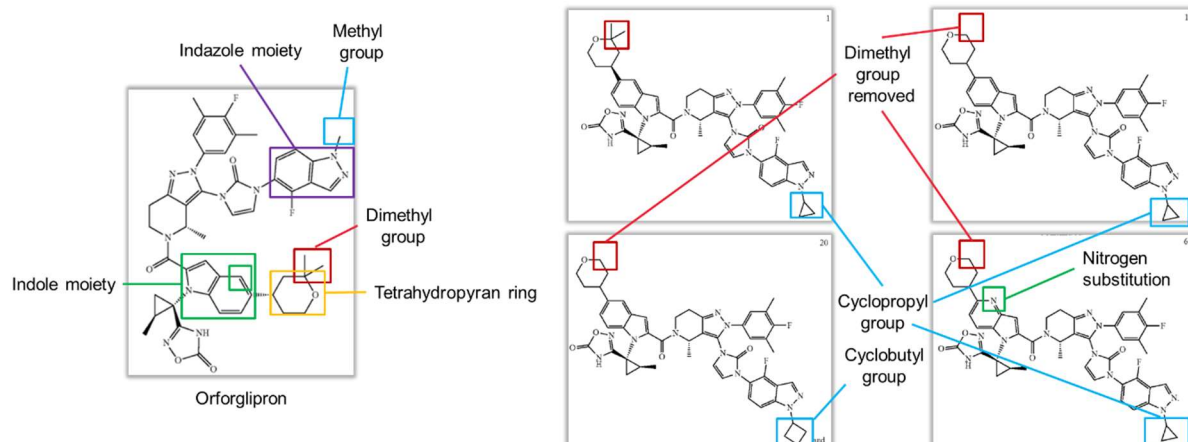
The chart below shows the compounds covered by each of the Challenged Claims:

Claim	Compounds Claimed
1 (Independent)	1, 13, 18, 19, 20, 21, 65
2	1, 13, 18, 19, 20, 21, 65 – Sodium, calcium, potassium, magnesium or lithium salt
3	1, 13, 18, 19, 20, 21, 65 – Sodium salt
4	1, 13, 18, 19, 20, 21, 65 – Hemicalcium salt
5	1, 13, 18
6	19, 20, 21
7	1
8	1 – Sodium salt
9	1 – Hemicalcium salt
12	19

Claim	Compounds Claimed
13	19 – Sodium salt
14	19 – Hemicalcium salt
15	20
16	20 – Sodium salt
17	20 – Hemicalcium salt
21	65
22	65 – Sodium salt
23	65 – Hemicalcium salt
24 (Independent)	1, 13, 18, 19, 20, 21, 65 – Compound only
25	1, 13, 18, 19, 20, 21, 65 – Pharmaceutical composition comprising compound and excipient

(EX1001, 204:10-220:58.) Petitioner only argues that Claimed Compounds 1, 19, 20 and 65 would have been obvious based on the prior art. (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. Challenged Compounds 19, 20 and 65 also have the dimethyl group on the tetrahydropyran ring removed. Compound 65 further has a nitrogen substitution at the 4-carbon on the benzene ring fused to the pyrrole ring. The image below shows the relevant groups and modifications in the Challenged Compounds.



(EX1008, 99 (Compound 67, 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.”). Consistent with that, the Challenged Compounds have unexpectedly superior properties compared to the prior art. (EX1001, 199:50-203:67.)

For instance, Compounds 19 and 20 demonstrate unexpectedly superior potency as compared to orforglipron and Compound 1 of the '236 Patent (which is the same as Su's compound 175). The specification discloses the results of an *in vitro* activity study showing that the potency of Compound 19 (as measured EC_{50}) nearly 3-fold greater than orforglipron and 7.8-fold greater than Compound 1:

TABLE 2	
Bioactivity of different compounds in hGLP-1R agonist cAMP stimulation assay	
Compounds	hGLP-1R CAMP: EC ₅₀ (nM)
1	0.094
13	0.228
18	0.265
19	0.012
20	0.018
21	0.044
24	0.868
29	0.063
35	0.025
36	0.05
37	0.06
55	0.15
65	0.092
66	0.014
70	0.064
76	0.019
77	0.022
78	0.012
79	0.171
80	0.038
81	0.042
82	0.011
84	0.08
50	0.028

(*Id.*, 201:1-27, Table 2 (annotated highlighted relevant compounds); *see also* EX2080 (showing EC₅₀ of 0.044 nm for orforglipron); EX2079, ¶123.)

The specification also shows that the Challenged Compounds had superior subcutaneous and oral pharmacokinetics as compared to prior art compounds.

TABLE 3			
Drug exposure of different compounds after a single-dose subcutaneous injection			
Compounds	Dosing route	Dose, mg/kg	AUC _{0-696h} , ng · h/mL
1	Subcutaneous	30	60,272
13	Subcutaneous	30	23,399
18	Subcutaneous	30	51,234
19	Subcutaneous	30	234,473
20	Subcutaneous	30	77,688
21	Subcutaneous	30	61,479
Orforglipron	Subcutaneous	30	5,390

TABLE 4

Pharmacokinetic parameters of different compounds after a single-dose oral administration				
Compounds	Dosing route	Dose, mg/kg	C_{max} , ng/ml	AUC_{0-48h} , ng · h/mL
19	Oral	5	4,460	60,043
20	Oral	5	1,900	16,982
65	Oral	5	10,993	71,836
Orforglipron	Oral	5	799	7,222

Note:

C_{max} refers to the maximum plasma concentration of a drug after administration

(EX1001, 201:31-202:50, Tables 3-4.) For instance, Table 3 shows that Challenged Compound 19 demonstrated an total drug exposure (AUC) more than **43-fold greater** than orforglipron and nearly **4-fold greater** than Compound 1 following a single-dose subcutaneous injection. (*Id.*, 201:31-67; EX2079, ¶124) Table 4 shows that Challenged Compound 19 has a maximum drug concentration (C_{max}) more than **5-fold greater** than orforglipron and an AUC more than **8-fold greater** than orforglipron following a single-dose oral administration. (EX1001, 202:37-50; EX2079, ¶124.)

During prosecution, the Examiner cited nearly all of the prior art relied on by Petitioner, including Yoshino, Kawai, Meng and Ren. (EX2002, 479-496, 681-836, 679, 686, 865-872.) The Examiner also considered numerous other references disclosing orforglipron derivatives. (EX2002, 681-836.) The Examiner ultimately allowed the claims, finding “Claims 1-25 are patentable over Yoshino” in the Notice of Allowance. (EX2002, 845.)

C. Ascletis Is Developing One of the Claimed Oral GLP-1R Agonists, Which Shows Great Promise for Treatment of Obesity

Ascletis is developing one of the claimed compounds, named ASC30, for treatment of obesity.¹ (EX2022; EX2066.) 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 recently announced topline results in its 13-week Phase 2 study evaluating ASC30, which continued to show promising safety and efficacy data, including a 7.7% mean reduction in body weight. (EX2042, 1-2; EX2079, ¶127.)

D. The Prior Art Discloses 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 they could have tried at numerous positions on the core structure of orforglipron.

Orforglipron was first disclosed in the patent applications that led to Petitioner's Yoshino reference. 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; EX2079, ¶72.) In addition to orforglipron, Yoshino discloses at least 158 additional

¹ Ascletis has not yet publicly disclosed which of the Claimed Compounds corresponds to ASC30.

exemplary compounds that include various modifications to the orforglipron core structure, including various substituents on the indazole and THP moieties. (*E.g.*, *id.*, Example Compounds 16, 126, 28, 26, 17, 120, 119, 30, 41, 61, 52, 77, and 113; EX2079, ¶75.) Notably, despite its plethora of potential substitutions, 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. (EX1008, 3:1-6:2, 5:21-67; EX2079, ¶74.) And, despite experimenting with numerous modifications on the THP moiety, Yoshino advanced only one compound, orforglipron, to pharmacokinetic studies. (EX1008, 312:61-313:34; EX1002, ¶72; EX2079, ¶77.) Orforglipron includes the dimethyl group on the THP moiety.

Su is a patent application that discloses derivatives of orforglipron. (EX1007, 4:10-40.)² Su includes a generic structure of GLP1-R agonists with hundreds of options for substituents, likely encompassing millions of potential compounds. (*Id.*, 5:1-7:4; EX2079, ¶79.) Su also discloses at least 218 working examples with various modifications to the core structure of orforglipron. (EX1007, 97:7-289:23; EX2079, ¶80.) In just those examples, Su discloses hundreds of potential modifications that could be mixed and matched to create innumerable potential compounds. (EX1007,

² Petitioner relies on both the published PCT Application No. PCT/CN2024/108192 (“Su”) and its provisional application CN 202311372605.9 (“Su II”). Only the disclosure of Su II is prior art to some of the Challenged Claims. Ascletis cites to Su II, but for ease of reference refers to it as Su.

97:7-289:23; EX2079, ¶¶79-80.) Critically, Su does not disclose biological activity data for any compound and only discloses pharmacokinetic data for five of its 218 working examples, none of which are the compounds relied on by Petitioner. (EX1007, 294:29-295:1; EX2079, ¶80.)

Meng is another patent application that discloses a large number of orforglipron derivatives. Meng includes a broad generic structure of GLP-1 receptor agonists likely encompassing millions of compounds. (EX1029, [0007] (cl. 1), [0009]-[0019]; EX2079, ¶99.) Meng discloses two exemplary compounds, Compounds (II) and (III), as well as potency data for both Compounds (II) and (III) compared to orforglipron. (EX1029, [0020]-[0021], [0186]-[0192]; EX2079, ¶103.) Without explanation, Petitioner relies exclusively on Compound (II) but the data shows that Compound (III) is more potent than both orforglipron and Compound (II). (EX1029, [0186]-[0192]; EX2079, ¶¶103-104.)

Ren is yet another patent application disclosing orforglipron derivatives. Like the previous references, Ren discloses a large genus of GLP1-R agonists likely encompassing millions of compounds. (EX1030, 3:51-67; EX2079, ¶105.) Ren discloses at least 103 exemplary compounds, as well as activity data on all 103 exemplary compounds and pharmacokinetic data on Compounds 19, 73, 76, 90, and 91 compared to orforglipron. (EX1030, 55-104, 457:53-460:30, Tables 29-30; EX2079, ¶107) The pharmacokinetic data disclosed in Ren demonstrates that,

among Compounds 19, 73, 76, 90, and orforglipron, Compound 73 has the best bioavailability. (EX1030, 459:60-460:10; EX2079, ¶109) Petitioner ignores Compound 73 completely and instead relies on Compound 90 to argue that the addition of a nitrogen in the benzene ring improves bioavailability. (Pet., 41-42; EX1002, ¶¶92-94.)

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 derivates, illustrating the plethora of potential modifications to orforglipron. (EX2002, 312-839; Pet., 11; EX2079, ¶128) 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, [1495]-[1519]; EX2079, ¶140.) WO 2023/016,546 discloses 150 additional orforglipron derivatives with biological activity for those compounds, as well as rat pharmacokinetic studies and glucose tolerance tests in non-human primates. (EX2020, 206:14-213:8; EX2079, ¶140.) WO 2024/153,070 (“Xu”) discloses yet another 63 exemplary orforglipron derivatives with biological activity data. (EX2021, [251]-[253]; EX2079, ¶140.) These examples provide just a sampling of the many references disclosing orforglipron derivatives (many with more available data than Su) and the numerous

paths that a skilled artisan seeking to modify orforglipron could have followed.
(EX2079, ¶141.)

E. Petitioner Filed a Patent Application with a Later Priority Date Claiming One of the Same Compounds It Now Says Is 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 Challenged Compounds. 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 discloses and individually claims Challenged 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).) The CSPC compound substitutes a cycloalkyl for the methyl on the orforglipron indazole moiety, one of the distinguishing features of all of the Challenged Claims. Clearly, when filing its application, Petitioner did not believe that substitution was obvious.

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-1R agonists. Now, having realized Ascletis invented the Challenged Compounds first, and unable to obtain a license, Petitioner has switched course and now asserts the Challenged Compounds were obvious all along.

III. LEVEL OF ORDINARY SKILL IN THE ART

A skilled artisan would have had a Bachelor's, Master's, or Doctoral degree in chemistry, medicinal chemistry, organic chemistry, pharmaceutical sciences, or a related field with one to three years of experience in small molecule drug discovery, including routine participation in compound synthesis, biological testing, and interpretation of SAR data, with a greater level of experience expected for a lower degree in education.

Patent Owner's proposed level of skill in the art substantively differs from Petitioner's proposal in the skilled artisan's number of years of experience. (*See* EX1002, ¶¶34-35 ("minimum of two to five years of experience").) Petitioner's proposed level of skill is too high, as the skilled artisan would be unlikely to have five or more years of experience in small molecule drug discovery. (EX2079, ¶131.) Nonetheless, a skilled artisan's conclusions would be the same no matter which level of skill were chosen, and Patent Owner's expert, Dr. Wipf, qualifies as a person of ordinary skill under both parties' definitions.

IV. 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.) The Board does not need to construe any terms to find the Challenged Claims not unpatentable.

V. PETITIONER HAS NOT PROVEN THAT ANY OF THE CHALLENGED CLAIMS WERE OBVIOUS

To avoid the risk of hindsight bias, Petitioner must “demonstrate both ‘that a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.’” *In re Magnum Oil Tools Int’l, Ltd.*, 829 F.3d 1364, 1381 (Fed. Cir. 2016). Petitioner does neither.

A skilled artisan seeking to modify orforglipron would have had innumerable options to try. The prior art discloses thousands of exemplary orforglipron derivatives with numerous positions that could be modified and innumerable potential modifications at each position. (§II.D; EX2079, ¶70.) Indeed, Yoshino alone discloses 14 plus positions for modification and thousands of potential substitutions on the indazole moiety. (EX2079, ¶73; EX1008, 3:1-6:2.)

In the face of these innumerable options, Petitioner does not articulate a single reason that a chemist would modify orforglipron. Petitioner, instead, contends that a skilled artisan would modify three specific positions in orforglipron, without any rationale for focusing on those positions to the exclusion of numerous other options. (Pet., 47-50, 84-86, 106; EX2033, 50:22-51:2, 59:3-17.) Petitioner then selects

specific modifications at each position that match the Challenged Compounds, even where the prior art has no data on those modification or data that shows a “significant” decrease in activity. (EX2079, ¶167; EX2033, 65:22-66:6.) Petitioner’s approach – starting with the structure of the Challenged Compounds and working backwards – is contrary to well-established law. *Otsuka Pharm. Co. v. Sandoz, Inc.*, 678 F.3d 1280, 1296 (Fed. Cir. 2012) (“The inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.”).

Petitioner also presents no analysis on reasonable expectation of success. The Petition only uses the word “expectation” four times and, even then, merely states that the prior art would give a skilled artisan such an expectation of success, without analysis. (Pet., 45, 56, 99, 116.) Such conclusory assertions are insufficient, particularly where small changes in structure can lead to significant, unpredictable changes in function. *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]”) (citation modified).

The objective evidence further shows the hindsight-driven nature of the Petition. Despite any structural similarities, the Challenged Compounds exhibit significantly improved potency, pharmacokinetic, and solubility properties

compared to orforglipron and Su's compounds. The prior art did not suggest those improvements, and they are even more surprising given companies' lack of success with small molecule GLP-1R agonists.

Below, we discuss the specific reasons why Petitioner has failed to meet its burden to show that any of the Challenged Claims are obvious.

A. Ground 1: Petitioner Fails to Show that Challenged Claim 19 is Obvious Over Su, Yoshino, Kawai and Talele

In Ground 1, Petitioner asserts that claims 1-4, 6, 12-14, 24, 25 are obvious as to Challenged Compound 19 over Su, Yoshino, Kawai and Talele. Petitioner does not come close to meeting its burden to show that Challenged Compound 19 is obvious by a preponderance of the evidence.

A skilled artisan would not choose Su Compounds 44 or 175 as lead compounds for further development.³ But, whether starting with one of those compounds or orforglipron (Yoshino), Petitioner provides no motivation to make the multiple changes needed to arrive at Compound 19. Nor does Petitioner establish a reasonable expectation of success. Moreover, Compound 19 shows significant

³ It is unclear if Ground 1 relies on orforglipron, Su's Compounds 44 or 175, or all of those compounds as leads. (*Compare* Pet., 53 ("A POSA seeking to modify orforglipron would have therefore been motivated ...", *with* Pet., 54 (showing a complicated chart with arrows starting at orforglipron, Su Compound 176, Su Compounds 175 and Su Compound 44).) We therefore address all three potential lead compounds.

unexpected results, further showing its non-obviousness, particularly considering others' failures in this area.

1. A Skilled Artisan Would Not Select Compound 44 or 175 of Su as a Lead Compound

In Ground 1, Petitioner appears to argue that a skilled artisan would select Compound 44 or Compound 175 as a lead compound for further modification. (Pet., 54-57.) Petitioner could not be more wrong.

“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.” *Otsuka Pharm.*, 678 F.3d at 1292. A lead compound is “a compound in the prior art that would be most promising to modify in order to improve upon its . . . activity . . .” *Takeda Chem.*, 492 F.3d at 1357. “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.” *Otsuka Pharm.*, 678 F.3d at 1292.

Su is but one reference disclosing potential modifications to orforglipron. (EX1007, 97:7-289:23.) As explained above, the prior art includes dozens of references disclosing millions of orforglipron derivatives, many of which included biological activity data for the disclosed compounds. (*See supra* §II.D; 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*** and limited pharmacokinetic data. *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. Nov. 29, 2022).

Even if they picked Su out of a hat, a skilled artisan would have no reason to select Compounds 44 and 175. Su does not include any data – potency, pharmacokinetic, or otherwise – for Compounds 44 and 175. (EX1007, 294:29-295:1; EX2079, ¶141.) In fact, Su advanced ***five different compounds*** (1, 3, 64, 173, and 174) to pharmacokinetic testing and discloses pharmacokinetic data for those compounds. (EX1007, 294:29-295:1; EX2079, ¶142.) As Dr. Wipf explains, if they relied on Su at all, a skilled artisan would focus on those compounds because Su’s data provides some information about their properties. (EX2079, ¶141.) At deposition, Dr. Pirrung agreed that compounds in a patent application that are “functionally characterized” with pharmacokinetic data, like Su Compounds 1, 3, 64, 173 and 174, are more likely “lead candidates” for further development. (EX2033, 61:1-63:6; EX2079, ¶280.) That’s because, without any data (as is the case for Su Compounds 44 and 175), a skilled artisan would have no way to assess the

effect of the substitutions made in those compounds. (EX2079, ¶142; EX2033, 75:15-78:16.) The Federal Circuit has routinely rejected proposed lead compounds in such circumstances. *Daiichi Sankyo Co., Ltd. v. Matrix Lab'ys, Ltd.*, 619 F.3d 1346, 1353-54 (Fed. Cir. 2010) (rejecting proposed lead compounds where the art lacked data on their activity but included such data for other compounds).

While completely ignoring Su's actual lead compounds, Petitioner and Dr. Pirrung contend that a skilled artisan would focus on Su Compounds 44 and 175 based on a convoluted theory that could only be the product of hindsight. (Pet., 51; EX1002, ¶¶61-67, 149-154.) That theory requires a skilled artisan:

1. Ignore the compounds in Su with pharmacokinetic data;
2. Focus instead only on the seven compounds that are "deuterated" (EX1002, ¶¶61-62, 149-151);
3. From those seven compounds, choose three that "share a common scaffold ring structure" to orforglipron (EX1002, ¶¶63-64, 152);
4. Then from those three compounds, choose Su Compounds 44 and 176 over Compound 35 because of a supposedly "less favorable[] change in electronic character," that is unsupported by any data or disclosure in Su (EX1002, ¶67; EX2033, 92:2-94:21);
5. Then, instead of deuterated compound 176, focus on its non-deuterated counterpart, Compound 175, despite Petitioner and Dr. Pirrung's assertion that deuteration was supposedly performed to improve metabolic function (EX1002, ¶¶62, 65, 153);

Petitioner's theory is fatally flawed at every step.

First, a skilled artisan would not focus on the compounds in Su that are “deuterated.” (EX2079, ¶144.) Petitioner asserts that a skilled artisan would understand the deuterated compounds to be of “particular interest” because of the time and effort associated with deuteration. (Pet., 52; EX2079, ¶144.) But Su does not explain why those compounds were deuterated, (EX1007), and both experts agree that deuteration is one way to try to improve metabolic function of compounds. (EX2079, ¶81; EX1002, ¶62.) Su does not include any data to show if the deuteration improved or worsened any metabolic properties of the compounds. (EX2079, ¶145; EX2033, 75:15-78:16.) Thus, if anything, a skilled artisan would understand that the deuterated compounds likely had some metabolic liability and would have no way to know whether the Su inventors fixed those problems. (EX2079, ¶145.) Instead, the skilled artisan would likely believe those compounds continued to be problematic given that Su ultimately chose to provide pharmacokinetic data on five different compounds, none of which were deuterated. (EX2079, ¶145.)

Second, Petitioner again uses hindsight to focus on three of the seven deuterated compounds (35, 44, and 176) because they have the same “common scaffold ring structure” as orforglipron. (Pet., 29-30, 53.) Notably, the five compounds advanced to pharmacokinetic testing in Su (and the only with any data) have significant structural changes from orforglipron and ***do not share*** its “common scaffold ring structure.” (EX2079, ¶¶145-146; EX2033, 79:23-80:2.) Petitioner does

not explain why a skilled artisan would only focus on compounds with the “common scaffold ring structure,” when Su focuses on compounds without that feature. *See Otsuka Pharm.*, 678 F.3d at 1292 (“In determining whether [skilled artisan] would have selected a prior art compound as a lead . . . mere structural similarity between a prior art compound and the claimed compound does not inform the lead compound selection.”). The only reasonable explanation is hindsight.

Third, Petitioner and Dr. Pirrung err in ignoring Su Compound 35 based on a supposed “less favorable[] change in electronic character” compared to Su Compounds 44 or 175. (EX1002, ¶67.) Neither Petitioner nor Dr. Pirrung explain why any change in electronic character caused by the substitution of the fluorine atom with a nitrogen atom would be “less favorable.” (EX1002, ¶67; Pet., 29-30; EX2033, 92:2-94:21.) In fact, a skilled artisan would have no way of knowing whether such a change would be favorable or unfavorable without making and testing the compounds and evaluating the data. (EX2079, ¶147.) Su does not provide any such data, and Dr. Pirrung admitted at deposition that he did not consider any data in forming his unsupported opinion on Su Compound 35. (EX2033, 92:2-93:1.) Petitioner’s exclusion of Compound 35 is nothing but more hindsight using the claimed structures as guides.

Next, Petitioner assumes that a skilled artisan would focus on Compound 175, which is the non-deuterated “parent” of Compound 176. (Pet., 54-55.) As Petitioner

itself argues, however, deuteration involves “labor-intensive synthetic procedures” that are “often examined to enhance metabolic traits of drug candidates.” (Pet., 29.) Su does not provide any data for Compounds 175 or 176 that would show a skilled artisan how deuteration affected the properties of those compounds. Petitioner does not explain why a skilled artisan would synthesize a deuterated compound to try to enhance its metabolic traits, only to then remove the deuterium atoms, particularly in the absence of data. Once again, the only explanation is hindsight.

In sum, Petitioner has not provided any credible reason why a skilled artisan would select Su out of the sea of orforglipron derivative prior art, much less focus on Compounds 44 or 175 as lead compounds. To the extent it relies on Su Compounds 44 or 175 as lead compounds, Ground 1 fails for that reason alone.

2. Petitioner Fails to Provide a Reason that a Skilled Artisan Would Modify Any of Its Lead Compounds

To avoid the risk of hindsight bias, Petitioner 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. Petitioner identifies no such reason to modify its apparent lead compounds in Ground 1, orforglipron and Su Compounds 44 and 175.

Petitioner and its expert, instead, repeatedly praise the attributes of orforglipron. Petitioner admits that orforglipron was “orally bioavailable” and

“exhibited full agonist efficacy . . . comparable to native GLP-1.” (Pet., 1, 9; EX1002, ¶¶48-49.) Further, Petitioner admits that orforglipron was “structurally optimized” for “once daily oral administration.” (Pet., 1; EX1002, ¶49.) Petitioner also acknowledges that “[c]linical data confirm that orforglipron significantly improves glycemic control and reduces body weight.” (Pet., 10; EX1002, ¶51.) In short, Petitioner and its expert indicate that orforglipron had strong potency and favorable pharmacokinetics.

As the experts agree, a skilled artisan would not seek to modify a compound such as orforglipron without identifying a characteristic or property to improve. (EX2079, ¶153; EX2033, 19:6-12.) For instance, Dr. Wipf explains that a medicinal chemist seeking to modify a known drug would first establish a “target compound profile” that identifies the specific properties desired for the modified compound. (EX2079, ¶47.) And Dr. Pirrung admitted in deposition that “[a] goal in a drug development program can be to make a compound better....” (EX2033, 19:6-12.)

Contrary to a skilled artisan’s approach, neither the Petition nor Dr. Pirrung’s expert declaration identifies any characteristic or property of orforglipron (or Su’s compounds) that a skilled artisan would purportedly seek to improve. (Pet., 1-2, 9-10; EX1002, ¶¶48-51.) They do not argue there was a need for improved potency or pharmacokinetics. (Pet., 1-2, 9-10; EX1002, ¶¶48-51.) Nor do they argue any other property needed to be improved.

Instead, Petitioner and Dr. Pirrung effectively argue that a skilled artisan would not be ***discouraged*** from making the substitutions in the claimed compounds. For instance, Petitioner argues that a skilled artisan would have understood from Kawai that the GLP-1R binding pocket “could accommodate bulkier substituents of hydrophobic nature without materially disrupting . . . the binding pocket.” (Pet., 35.) Likewise, Petitioner argues that a skilled artisan would understand that certain modifications to orforglipron would “maintain” or “preserve” biological activity. (Pet., 60, 63, 64.) Instead, Petitioner and Dr. Pirrung effectively argue that a skilled artisan would not be ***discouraged*** from making the substitutions in the claimed compounds. But “[t]he 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.’” *Adidas AG v. Nike, Inc.*, 963 F.3d 1355, 1359 (Fed. Cir. 2020). For that reason, the Federal Circuit has routinely rejected obviousness challenges that rely on a general motivation to just make more compounds, like Petitioner’s argument here. *See Takeda Pharm. Co. Ltd.*, 844 F. App’x at 342 (citation modified) (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].”); *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”).

Because Petitioner fails to provide a specific motivation to modify orforglipron, its obviousness argument for Compound 1 must fail.

3. Starting with Orforglipron, Petitioner Fails to Prove that a Skilled Artisan Would be Motivated to Make the Substitutions in Compound 19

A skilled artisan would need to make three changes to orforglipron to arrive at Compound 19. First, the skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl group. Second and third, the skilled artisan would have to remove each of the two methyl groups on the tetrahydropyran (“THP”) moiety of orforglipron. Petitioner failed to show that a skilled artisan would be motivated to make those changes.

i. No Motivation to Replace the Methyl on the Indazole Moiety of Orforglipron with Cyclopropyl

A skilled artisan would not be motivated to replace the methyl group on the indazole moiety of orforglipron with a cyclopropyl group. As discussed above, Petitioner has not explained the skilled artisan’s alleged objectives in modifying orforglipron. (§V.A.2.) But whatever their supposed goal, a skilled artisan would know that there were many positions for potential modification or substitution on orforglipron. (EX2079, ¶191.) The indazole group on orforglipron, and its methyl specifically, was no more than a needle in a haystack among these options.

Among all the choices, a skilled artisan would not have been particularly motivated to substitute the methyl group on the indazole moiety with alternate substituents because of the so-called “magic methyl effect.” Methyl groups are understood to have an outsized impact on a molecule’s potency, selectivity, conformation and pharmacokinetics. (EX2079, ¶52; EX2028, Abstract.) Thus, absent a clear prior art teaching, the methyl group on the indazole moiety would not be the first place that a skilled artisan would have sought to modify orforglipron. As explained below, Petitioner’s prior art does not include any such teaching.

Yoshino. Yoshino would not motivate a skilled artisan to replace the methyl group on the indazole moiety with cyclopropyl. Indeed, despite disclosing numerous compounds with substitutions on the indazole moiety of orforglipron Yoshino does not disclose a cycloalkyl group at that position. (EX2079, ¶74.)

Yoshino, in fact, teaches away from substituting a cycloalkyl for the methyl group on the indazole moiety. Yoshino’s generic Formula (I) covers thousands, if not millions, of potential GLP-1R agonists, including eleven broad categories of possible substituents on the indazole moiety (Z^2). (EX2079, ¶73; EX2033, 58:21-59:17.) Despite this vast number of options, ***Formula (I) does not allow for cycloalkyl groups*** as substituents for the indazole moiety.⁴ Yoshino also discloses

⁴ While Yoshino includes cycloalkyl as an option for Z^2 itself (EX1008, 5:21-26), it does not list cycloalkyl as an option for the allowed ***substituents on the Z^2 group***.

159 exemplary compounds, none of which include a cycloalkyl substituent. (EX2079, ¶75.) A skilled artisan would understand Yoshino's exclusion of cycloalkyl groups as substituents on Z² to be an intentional choice teaching away from that modification. *Eli Lilly & 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).

Despite Yoshino's exclusion of cycloalkyl groups, Petitioner incorrectly argues that Yoshino suggests replacing the methyl group with a cycloalkyl because certain exemplary compounds include a tetrahydrofuran ("THF") ring. (Pet., 59-61; EX1002, ¶¶160-163.) Petitioner is wrong for at least two reasons.

First, Yoshino does not teach that substituting a THF ring on the indazole moiety of orforglipron is beneficial. Of the exemplary compounds that include substitutions on the indazole moiety, structures with a THF ring moiety have considerably lower activity than orforglipron. (EX1008, Table 3 (*compare* Compounds 8 (2.5 nM), 14 (2.3 nM), 22 (2.3 nM), 40 (2.2 nM), 64 (2.0 nM) *with* Compound 67 (1.2 nM)); EX2079, ¶76; EX2033, 65:16-66:6 (acknowledging that

(EX1008, 5:21-6:2.) Moreover, although the Z² substituents include "C₁₋₆ alkyl" and "3 to 12 membered heterocyclyl," the patent defines those terms to exclude cycloalkyl groups (EX1008, 5:21-6:2, 9:56-62, 10:39-64; EX2079, ¶¶73-74.)

Compound 40 has a 1.8 fold lower potency than orforglipron).) For instance, Yoshino's Compound 40, which Dr. Pirrung characterizes as having "comparable activity" to orforglipron, actually has a nearly two-fold **decrease** in activity. (EX1002, ¶160; EX1008, Table 3 (*contrast* Compound 67 (1.2 nM) *with* Compound 40 (2.2 nM)).) At deposition, Dr. Pirrung was forced to admit that decrease in activity was in fact "significant." (EX2033, 65:16-66:6 (acknowledging that Compound 40 has a 1.8-fold lower potency than orforglipron and is a "significant difference").) In contrast to that "significantly" lower activity, compounds in Yoshino without a THF ring have up to two times **greater** activity than orforglipron. (EX1008 (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 would be motivated to modify orforglipron with a substituent that leads to a "significant" decrease in activity, while ignoring other modifications that lead to increased activity.⁵ The only credible reason is the improper use of hindsight. *Tec Air, Inc. v. Denso Mfg. Mich. Inc.*, 192 F.3d 1353, 1360 (Fed. Cir. 1999) (teaching away where reference would have led a POSA "in a direction divergent from the path taken by the applicant").

⁵ Yoshino also does not provide pharmacokinetic data for any of its THF ring-containing compounds. (EX1008, Table 3.) A skilled artisan thus would have no way to assess if or how the THF ring on the indazole moiety affected the pharmacokinetic properties of orforglipron derivatives. (EX2079, ¶225.)

Second, cycloalkyl groups and THF rings have different properties and often have different effects as substituents. (EX2079, ¶166.) THF rings include an oxygen atom, which makes them moderately polar, whereas cycloalkyls, such as cyclopropyl, include only carbon and hydrogen atoms and are non-polar. (*Contrast* EX2024 *with* EX2025; EX2079, ¶166; EX2033, 64:2-65:2.) A skilled artisan would understand that polar substituents are likely to have different interactions with a receptor than non-polar substituents and, thus, would not consider the two interchangeable, or expect them to have similar effects as a substituent. (EX2026, 2; EX2027, 2-6; EX2033, 63:13-25.) As a result, even if Yoshino motivated a skilled artisan to substitute a THF ring for the methyl on the indazole moiety, it does not follow that a skilled artisan would be motivated to substitute a non-polar cycloalkyl group in that position, particularly given Yoshino’s exclusion of such groups.

Kawai. Kawai likewise would not motivate a skilled artisan to substitute the methyl on indazole with a cycloalkyl. Kawai merely provides a “high resolution structure” of orforglipron “in complex” with the GLP-1 receptor using cryoelectron microscopy (“cryo-EM”). (EX1004, Fig. 1I, 8.)

Kawai does not suggest making any modification to orforglipron. To the contrary, Kawai praises orforglipron (LY3502970), noting that it “displays a preclinical pharmacodynamic profile similar to marketed peptide-based GLP-1R

agonists and possesses pharmacokinetic properties compatible with oral dosing in humans.” (EX1004, 7; EX2079, ¶84.) Kawai makes no mention of a cycloalkyl.

Petitioner, based solely on the testimony of Dr. Pirrung, incorrectly argues that Kawai would motivate a skilled artisan to substitute cyclopropyl for methyl on the indazole moiety of orforglipron. (Pet., 34-35, 57-58; EX1002, ¶¶57-59, 157-159.) Dr. Pirrung’s opinion is flawed for multiple reasons.

First, Dr. Pirrung bases his opinion on Kawai providing “a valuable framework for structure-based drug design, particularly in evaluating potential modifications to orforglipron.” (EX1002, ¶¶59, 156-157; Pet., 35, 57.) But Dr. Pirrung admitted at deposition that he has never engaged in “structure-based drug design” once over the course of his 40-year career. (EX2033, 11:10-13:23.) Dr. Pirrung’s testimony should thus be given little weight on this issue. *Chevron Oronite Co. LLC v. Infineum USA L.P.*, No. IPR2018-00922 (P.T.A.B. Nov. 6, 2019), *aff’d*, 2022 WL 3147683 (Fed. Cir. 2022) (giving expert testimony less weight where the expert lacked formulation experience in determining the patentability of claims directed to lubrication oil formulations).

Second, Dr. Pirrung incorrectly contends that Kawai discloses that “the [GLP-1R] binding pocket adjacent to the methyl group of the indazole moiety” is “spacious” and could accommodate a “bulkier” substituent. (Pet., 34-35, 58; EX1002, ¶¶58, 159.) Kawai says nothing about a “spacious environment”

surrounding the indazole moiety or “bulkier substituents.”⁶ (EX1004.) Indeed, if anything, Kawai suggests that a bulkier substituent on the indazole moiety could have negative consequences because “the 4-fluoro-1-methyl-indazole moiety” has “aromatic interactions with Tyr205 and Tyr145.” (EX1004, 4.) As Dr. Wipf explains, a bulkier substituent could disrupt those stabilizing aromatic interactions and lead to worse properties. (EX2079, ¶96; EX1002, ¶158.)

Dr. Pirrung’s opinion that the binding pocket is “spacious” is further flawed because it is primarily based on a two-dimensional image of the cryo-EM model in Kawai. (EX1002, ¶159; Pet., 51; EX2033, 37:8-38:16.) Despite admitting at deposition that a skilled artisan would have had access to the full three-dimensional cryo-EM model in Protein Data Bank,⁷ Dr. Pirrung did not look at the three-dimensional model in forming his opinions. (EX2033, 35:10-36:9.) As Dr. Wipf explains, the full three-dimensional cryo-EM model shows that the methyl group fits well in the relevant binding pocket on the GLP-1 receptor but not that there is additional space to accommodate a bulkier substituent. (EX2079, ¶92.)

⁶ Kawai refers to the “conformational flexibility of GLP-1R and GPCRs *in general*” (EX1004, 4 (emphasis added)) but not to the flexibility or space in the binding pocket adjacent the methyl group on the indazole moiety.

⁷ Kawai indicates that the full three-dimensional cryo-EM model of orforglipron bound to the GLP-1 receptor was deposited in Protein Data Bank, a public database. (EX1004, 8; EX2079, ¶88.) The 3D structure can be manipulated, such that skilled artisans can visualize specific interactions on receptors and calculate distances between side chains of a receptor and drug compound moieties. (EX2079, ¶95.)

Third, Dr. Pirrung is further wrong that Kawai shows that the environment surrounding the methyl group of the indazole moiety is “hydrophobic,” such that it would favor “substituents of hydrophobic nature,” like cyclopropyl. (EX1002, ¶159; Pet., 34-35.) As Petitioner admits, Kawai discloses that the region surrounding the methyl group on the indazole moiety is formed by the amino acids tyrosine, glutamate, and lysine. (Pet., 58; EX1004, FIG 1I.) Two of those amino acids (glutamate and lysine) are polar and the other (tyrosine) has portions that are polar (hydrophilic) and portions that are non-polar (hydrophobic) (EX2079, ¶177; EX2033, 39:13-41:3, 42:17-43:6, 45:15-46:7.) Based on that information alone, a skilled artisan would suspect the environment surrounding the methyl group on the indazole moiety would be polar in nature and favor polar substituents, not non-polar substituents, like cyclopropyl. (EX2079, ¶178.)

Dr. Pirrung, once again, incorrectly relies on the two-dimensional image in Kawai to reach a different conclusion. (EX1002, ¶159.) But, as Dr. Wipf explains, a skilled artisan would look at the three-dimensional model in Protein Data Bank to measure the distances between the polar and non-polar groups of the GLP-1R binding pocket and the methyl group on the indazole moiety. (EX2079, ¶178.) That analysis shows that the polar carboxylic acid group of the glutamate amino acid is the closest functional group to the methyl on the indazole moiety and that the non-polar groups on the tyrosine moieties do not meaningfully interact with the methyl

group.⁸ (EX2079, ¶178.) As a result, the skilled artisan would understand that the environment surrounding the methyl group on the indazole moiety is polar and thus favors polar, hydrophilic substituents, rather than non-polar, hydrophobic substituents, like cyclopropyl. (EX2079, ¶181.)

Because it says nothing about modifying orforglipron, does not mention cycloalkyl substituents, and does not show that the relevant binding pocket is either “spacious” or “hydrophobic,” Kawai does not provide any reason for a skilled artisan to modify the indazole moiety of orforglipron, much less to substitute a cyclopropyl for the methyl group.

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.)

Talele has nothing to do with GLP-1R agonists, generally, or orforglipron, specifically. (EX1009.) 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,

⁸ Dr. Pirrung conceded at deposition that he made no attempt to determine how close any of the polar or non-polar amino acid groups were to the methyl on the indazole moiety. (EX2033, 39:13-46:15.) Instead, Dr. Pirrung assumed the environment would be hydrophobic based on the two-dimensional image in Kawai. (EX2033, 42:9-15, 43:7-45:7.)

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 U.S., LLC v. Dr. Reddy's Lab 'ys, Inc.*, 933 F.3d 1367, 1378 (Fed. Cir. 2019) (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").

As Dr. Pirrung agreed, a cyclopropyl group is merely one of many tools in the medicinal chemist's toolkit that may or may not work depending on the context. (EX2033, 97:22-99:5 (affirming that "there are other strategies of course for lead optimization" besides cyclopropyl.) Consistent with his testimony, 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). (EX2079, ¶188; 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.

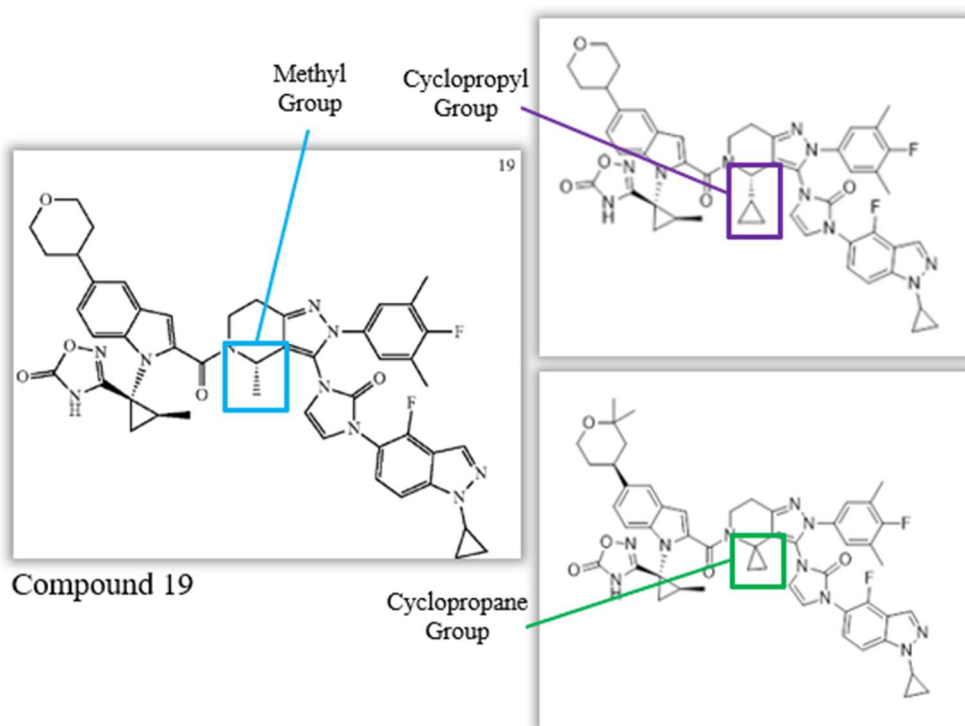
Petitioner argues that Talele generically teaches that cyclopropyl rings can “enhanc[e] metabolic stability, improv[e] pharmacokinetic properties, or modulat[e] the biological activity of a drug molecule.” (Pet., 62; EX1002, ¶167.) But Petitioner does not point to any suggestion in the prior art that orforglipron has any shortcoming with any of those properties. Rather, Petitioner admits that orforglipron was “structurally optimized” for “once daily oral administration” and calls orforglipron a “promising candidate.” (Pet., 1-2; EX1002, ¶¶49-51.) These are hallmarks of good metabolic stability, pharmacokinetics, and biological activity, not suggestions of need for improvement.

Talele also discloses that cyclopropyls may or may not lead to improved properties depending on the context. (EX1009, 20, 24.) After discussing examples where cyclopropyls led to substantially *worse* properties, Talele cautions that “PK properties can be modulated with a cyclopropyl group” but “it is context dependent and one strategy does not work in all cases.” (EX1009, 20; EX2079, ¶184.)

Talele’s caution that the effect of a cyclopropyl substitution is “context dependent” is consistent with the realities of drug development. As Dr. Wipf explains, a skilled artisan would know that a cycloalkyl might improve, might make worse, or might have little effect on the properties of any compound, depending on the specific compound and target. (EX2079, ¶187; EX2074, 2.) Dr. Pirrung similarly admitted in deposition that “there are examples where introducing a [cyclopropyl] is

not . . .beneficiary as any structural change that is part of the tool box of the medicinal chemist does not work in every single example.” (EX2033, 97:22-98:7.)

That unpredictability is further shown by Ascletis’s own synthesis and testing of orforglipron derivatives that substitute a methyl group with a cyclopropyl group. (EX2080, 4; EX2079, ¶¶185-186.) Specifically, Ascletis synthesized two compounds not explicitly disclosed in the ’236 Patent in which a cyclopropyl or cyclopropane group was substituted for a methyl group at an additional position on Compound 19, as shown below.



(EX2080, 4; EX2079, ¶185.) The cyclopropyl substitutions significantly decreased potency in both compounds compared to orforglipron and Challenged Compound 19, with one of the compounds losing activity completely. (EX2080, 4.) A skilled

artisan thus would have understood that adding a cyclopropyl was one of many possible modifications that would not always result in a compound with desirable properties. (EX2079, ¶187.)

Because Petitioner has not shown that Yoshino, Kawai, and/or Talele would motivate a skilled artisan to substitute a cyclopropyl group for the methyl on the indazole moiety, Petitioner has not shown that Compound 19 is obvious based on Ground 1 starting with orforglipron.

ii. No Motivation to Remove the Dimethyl Group on the THP Moiety of Orforglipron

Petitioner has further failed to show that a skilled artisan would be motivated to also remove each of the two methyl groups on the THP moiety of orforglipron. Petitioner points to Yoshino and Compound 44 of Su as supposedly encouraging the removal of each methyl group from the THP moiety of orforglipron (Pet., 54-57, 63-64) but neither does. (Pet., 54-57, 63-64.)

To start, a skilled artisan would know that there were many positions for potential modification or substitution on orforglipron. (EX2079, ¶191.) The THP moiety on orforglipron was no more than one of numerous positions where a skilled artisan could have experimented with orforglipron.

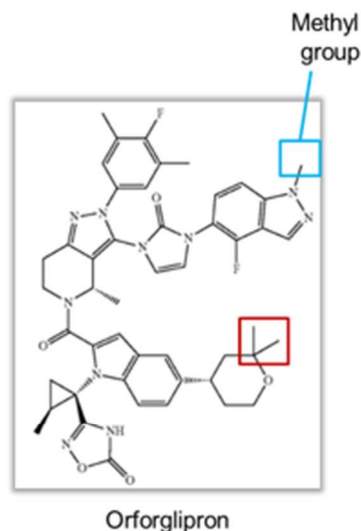
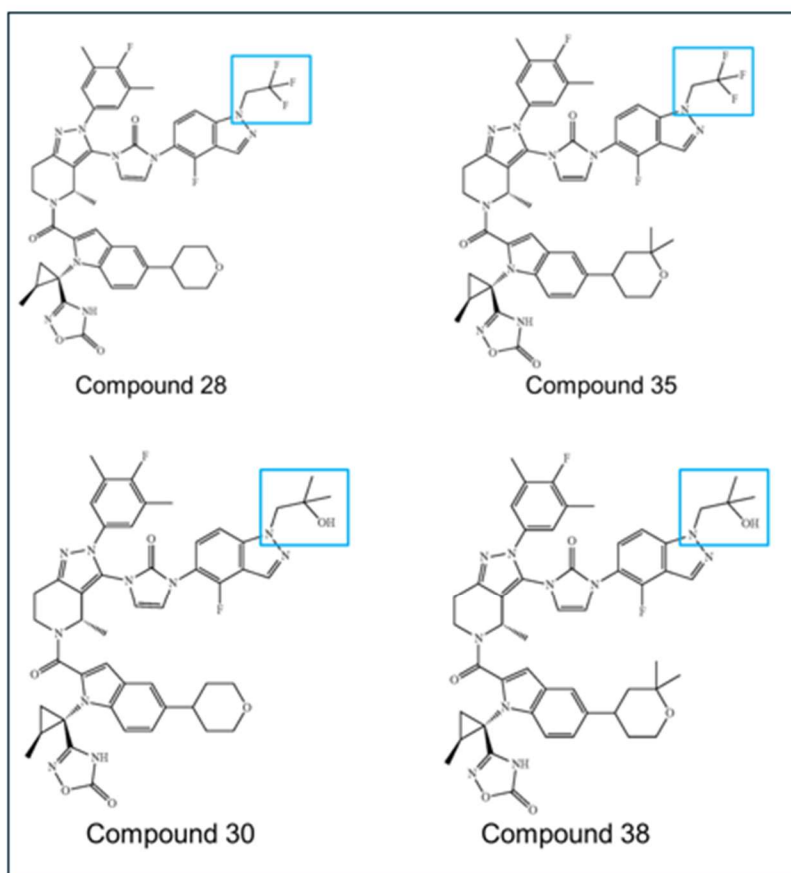
Of the potential positions for modification, a skilled artisan would not have prioritized the THP moiety. The three-dimensional cryo-EM structure disclosed in

Kawai and deposited in the Protein Data Bank shows that the dimethyl group on the THP moiety fits well in the binding pocket of the GLP-1 receptor. (EX2079, ¶¶197-198.) A skilled artisan would suspect that removing the dimethyl group would reduce the fit in this region of the binding pocket and decrease the structural complementarity between the receptor protein and orforglipron. (EX2079, ¶198.) Thus, without any particular reason to make the change, a skilled artisan would be discouraged from removing the dimethyl group on orforglipron's THP moiety. As explained below, Petitioner's prior art does not include any such motivation.

Yoshino. Petitioner opines that Yoshino Compounds 28 and 30, which remove the dimethyl group on the THP moiety, “maintain biological activity” and thus would encourage a skilled artisan to make that substitution. (Pet., 63.) Petitioner's argument fails for multiple reasons.

First, Petitioner does not explain why a skilled artisan would focus on the modifications in Compounds 28 and 30 because they supposedly “maintain” activity. (Pet., 63.) Absent the benefit of hindsight, a skilled artisan would not have been motivated to make such a modification. *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[.]”)

Second, both Compounds 28 and 30 have additional modifications compared to orforglipron that could affect their properties, as shown below.



(EX2079, ¶194.) A skilled artisan would not be able to assess the effect of removal of the dimethyl group on the THP moiety relative to orforglipron given the other differences in the molecules. (EX2079, ¶194.) In other words, a skilled artisan could not determine from Yoshino if any change in potency was due to the removal of the dimethyl group or the change in the other substituent. (*Id.*)

Third, many of the other examples in Yoshino that remove the dimethyl group on the THF moiety in fact have **decreased** potency. Among the 80 compounds with potency data in Yoshino (Table 3), 30 possess a THP ring, many of which do not retain potency compared to orforglipron. (EX1002, ¶169; EX2079, ¶195.) For

example, Yoshino's Compound 25 has an EC_{50} of 4.0 nM, and Yoshino's Compound 57 has an EC_{50} of 8.1 nM, compared to orforglipron's 1.2 nM. (EX1008, 310:41-311:51; EX2079, ¶195.) A skilled artisan would understand from this data that compounds without the dimethyl group may in fact lead to worse pharmacological properties. (EX2079, ¶195.)

Fourth, Yoshino chose to move forward with orforglipron (Compound 67), which includes the dimethyl group on the THP moiety, despite extensive experimentation with different THP moiety substitutions. (EX1008, 311:51-313:34.) In addition to 30 compounds with the dimethyl group removed, Yoshino also discloses numerous compounds with THP moiety substitutions besides dimethyl. (EX2079, ¶196; EX1008, 31-55, 89-90, 92-101, 120-121, 133-161.) Despite that experimentation, Yoshino advanced orforglipron, with the dimethyl group on the THP moiety, to pharmacokinetic studies. (EX1008, 311:51-313:34.) A skilled artisan would understand Yoshino likely believed the dimethyl group provided superior properties, particularly because it is more difficult to synthesize a THP ring with a dimethyl substitution than without it. (EX2079, ¶196.)

Yoshino thus would not motivate a skilled artisan to remove the dimethyl group on the THP moiety of orforglipron.

Su. Su further does not provide any motivation to remove the dimethyl group on the THP moiety. Petitioner and Dr. Pirrung argue that Compound 44 would

encourage a skilled artisan to remove the dimethyl group on the THP ring. (Pet., 55-56; EX1002, ¶154.) Su does not disclose any data for Compound 44, and a skilled artisan would not have any reason to focus on Compound 44 when Su discloses data for other compounds. (§V.A.1; EX2079, ¶142.) Moreover, unlike Challenged Compound 19, the THP ring on Compound 44 is substituted with two deuterium atoms. Su does not disclose a non-deuterated version of Compound 44, nor suggest that deuteration is unnecessary. (EX2079, ¶¶207-208; EX1007.)

iii. No Motivation to Make Both Changes

Even if it had shown a skilled artisan would be motivated to substitute the methyl group on the indazole with a cyclopropyl or remove both methyl groups from the THP moiety, Petitioner does not articulate any motivation for a skilled artisan to make both modifications to orforglipron in the same compound. Rather, Petitioner states that “these two routine and predictable modifications would have resulted in claimed Compound 19” when combined, without any further explanation. (Pet., 97, *see also id.*, 64.) Because such conclusory analysis is “fraught with hindsight bias,” Ground 1 must fail with orforglipron as lead. *ActiveVideo Networks, Inc. v. Verizon Commc’ns, Inc.*, 694 F.3d 1312, 1327 (Fed. Cir. 2012).

4. Starting with Su, Petitioner Does Not Establish a Motivation to Make the Substitutions in Compound 19

Petitioner fares no better starting with Su Compounds 44 or 175. From Su Compound 44, a skilled artisan would have to substitute a cyclopropyl for the methyl

group on the indazole moiety *and* remove both deuterium atoms from the THP moiety. Starting with Su Compound 175, a skilled artisan would need to remove both methyl groups from the THP moiety. Petitioner has not shown that a skilled artisan would have been motivated to make those changes.

i. No Motivation to Combine Su Compounds 44 and 175.

To start, Su itself does not provide any motivation to combine Compounds 44 or 175. Notably, despite experimenting with both of them, Su itself does not make the substitutions seen in Su Compounds 44 and 175 in one compound. (EX1007; EX2079, ¶202.) Nor does Su provide any explicit suggestion to combine those compounds. (EX1007; EX2079, ¶202.)

Petitioner likewise does not provide any rationale for combining Su Compounds 44 and 175. The Petition only conclusively states in passing that a skilled artisan would have been “motivated to implement the [modification of Compound 44] to Compound 175.” (Pet., 57.) But neither Petitioner nor Dr. Pirrung provide any reason why a skilled artisan would implement such modifications.

A skilled artisan would not be motivated to combine Su Compounds 44 and 175 because Su provides no data for them. (§V.A.3.iii.) For the same reasons they would not select Compounds 44 and 175 as lead compounds, a skilled artisan would not be motivated to combine the substitutions made in the two compounds.

(§V.A.3.iii; EX2079, ¶203.) In short, a skilled artisan could not assess the effect the respective substitutions made in Su Compounds 44 and 175 given the lack of data and would not have any reason to think making both substitutions in one compound would be beneficial. *Daiichi*, 619 F.3d at 1353-54 (“**Potent and promising activity in the prior art trumps** mere structural relationships.”) (emphasis added).

Even if Su’s Compounds 44 and 175 were combined, a skilled artisan would need to remove the deuterium atoms from the THP moiety to achieve Challenged Compound 19. Su does not motivate a skilled artisan to make that change. Despite disclosing deuterated and non-deuterated versions of certain other compounds, Su does not present a non-deuterated version of Compound 44. (EX1007; EX2079, ¶208.) Nor does Su explain why Compound 44 was deuterated or suggest that deuteration is unnecessary. (EX2079, ¶208.) Indeed, Dr. Pirrung opines that Su likely deuterated Compound 44 to try to enhance its metabolic activity but fails to explain why a skilled artisan would then think that **removing** those same deuterium atoms would be beneficial. (EX1002, ¶154; EX2079, ¶209.) Moreover, Dr. Pirrung’s opinion that removing the deuterium atoms could offer synthetic simplicity is not a sufficient motivation to modify Compound 44. *Eli Lilly & Co.*, 471 F.3d at 1378 (“[P]atentability for a chemical compound does not depend only on structural similarity. . . Th[e] court will not ignore a relevant property of a compound in the obviousness calculus.”).

Petitioner does not provide any rationale for combining Su Compounds 44 and 175 to arrive at Challenged Compound 19. The Petition only conclusively states in passing that a skilled artisan would have been “motivated to implement the [modification of Compound 44] to Compound 175.” (Pet., 57.) But neither Petitioner nor Dr. Pirrung provide any reason as to why a skilled artisan would implement such modifications, particularly where Su does not disclose the combination itself or provide any data indicating that the combination would be beneficial.

ii. No Motivation to Modify Compound 44 to Replace the Methyl on the Indazole Moiety with Cyclopropyl

Starting with Su’s Compound 44, a skilled artisan would have to substitute a cyclopropyl for the methyl on the indazole moiety *and* remove the deuterium atoms from the THP moiety to make Challenged Compound 19. Petitioner has failed to establish a motivation to make either modification.

For the same reasons explained above, Yoshino, Kawai, and Talele would not motivate a skilled artisan to replace the methyl group on the indazole moiety with cyclopropyl. (§V.A.3.i; EX2079, ¶210.)

Moreover, nothing in Yoshino, Kawai or Talele suggests removing the two deuterium atoms from Su Compound 44. (§V.A.3.ii.) As explained above, Yoshino discloses 30 compounds in which the THP ring is not substituted, the majority of which exhibit worse potency than orforglipron. (EX1008, 310:41-311:51.) Kawai

makes no comment or disclosure regarding the dimethyl group on the THP moiety, and as explained above, a skilled artisan analyzing the cryo-EM structure would understand that the dimethyl group fits well in binding pocket of the protein receptor. (§V.A.3.ii.) And Talele has no teachings regarding the removal of the dimethyl group. Nothing in those references provides a motivation to remove the deuterium atoms from Su's Compound 44. (§V.A.3.ii.)

iii. No Motivation to Remove the Dimethyl Group from the THP Moiety of Su Compound 175

Starting with Su Compound 175, Petitioner had to show that a skilled artisan would be motivated to remove the dimethyl group from the THP moiety to arrive at Challenged Compound 19. Petitioner again has failed to meet its burden. For the same reasons discussed above in Section V.A.3.ii, Yoshino, Kawai, and Talele would not motivate a skilled artisan to remove the dimethyl group on the THP.

5. Petitioner Has Not Shown that Compound 19 Is Unpatentable as Obvious-to-Try

To the extent the Petition advances an obvious-to-try rationale, Petitioner likewise fails to meet its burden.

To establish an invention was obvious-to-try, Petitioner had to show a “a finite number of identified, predictable solutions[.]” *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 419-22 (2007). When “what would have been ‘obvious to try’ would have been to . . . try each of numerous possible choices until one possibly arrived at a

successful result” an invention would not have been obvious. *Bayer Schering Pharma AG v. Barr Lab’ys, Inc.*, 575 F.3d 1341, 1347 (Fed. Cir. 2009) (citing *In re O’Farrell*, 853 F.2d 894, 903 (Fed. Cir. 1988)). In the absence of such predictability, Petitioner’s focus on specific disclosures from the prior art, selected from numerous possible alternatives to arrive at the claims, speaks to hindsight reasoning, rather than obviousness. *In re Kubin*, 561 F.3d 1351, 1359 (Fed. Cir. 2009) .

As the prior art shows, there were a nearly infinite number of potential modifications to orforglipron. (EX2079, ¶214.) The prior art discloses thousands of orforglipron derivates and generic formulas that provide an endless supply of design choices. (EX2079, ¶215; EX1008, 3:1-6:2; EX1007, 5:1-7:4; EX1029, [0007]; EX1030, 3:51-67.) There were many positions on orforglipron that a skilled artisan could have attempted to modify, not only the positions that Petitioner focuses on with hindsight. (EX2079, ¶216.) Even if a skilled artisan focused on the positions modified in the Challenged Compounds, the asserted prior art discloses thousands of possible options for each position. (EX2079, ¶217.) Nothing in the asserted prior art points a skilled artisan to any one particular modification. Rather, a skilled artisan would understand that there are limitless possibilities to choose from, synthesize, and test.

Moreover, as discussed below, none of the multitude of possible design alternatives were predictable. (§V.6; EX2079, ¶219.) To the contrary, small changes

in drug design can lead to big and unpredictable changes in properties. (§V.6; EX2079, ¶49.) Therefore, Challenged Compound 19 would not have been obvious to try.

6. Petitioner Fails to Establish a Reasonable Expectation of Success of Achieving Compound 19

Petitioner also fails to establish a reasonable expectation of success for achieving Challenged Compound 19. Indeed, the Petition only uses the word “expectation” four times in the Petition, (Pet., 45, 56, 99, 116), and merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success, without analysis. (Pet., 45, 56, 99, 116.) Dr. Pirrung likewise offers no analysis of reasonable expectation of success for Compound 19. (EX1002, ¶¶152-154, 225, 312.)

In the chemistry context, the challenger must show that a skilled artisan would reasonably expect the compound to achieve the desired 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.”). Merely showing that a chemist could make the claimed compound is insufficient. *Pfizer Inc.*, 555 F. App’x at 971 (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]”) (citation modified).

Petitioner does not identify any particular properties of orforglipron that a skilled artisan would seek to improve. (EX2079, ¶222.) Further, Petitioner does not offer any analysis to establish that a skilled artisan would reasonably expect the claimed compounds to actually result in whatever (unidentified) properties a skilled artisan would purportedly seek in modifying orforglipron. (*Id.*)

Moreover, nothing in the prior art suggests that Challenged Compound 19 would have desirable properties. Because Su does not include any data on Su Compounds 44 and 175, a skilled artisan would have no way to assess the effect of the modifications, much less a reasonable expectation that Compound 19 would have any desirable properties. (EX2079, ¶224.) Likewise, Yoshino does not provide a reasonable expectation that Compound 19 would achieve desirable properties

because it teaches away from a cyclopropyl substitution on the indazole moiety, suggests that compounds without a dimethyl group on the THP moiety have reduced activity compared to orforglipron, and only has pharmacokinetic data on orforglipron. (EX2079, ¶225.) Further, Kawai only has pharmacokinetic data on orforglipron, and Talele has nothing to do with GLP-1R agonists; therefore neither provides a reasonable expectation that Compound 19 would achieve any desirable properties. (EX2079, ¶226.) Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compound 19 based on the prior art.

Moreover, as Dr. Wipf explains, a skilled artisan would understand that small structural changes to orforglipron can result in big differences in properties. For example, a single methyl group added to a compound can inhibit or improve activity for a compound depending on the position of the addition. (EX2079, ¶227; EX2034, 111, Fig. 11.14.) There would be no way of knowing the effect of the change, however, or whether it is successful in achieving desired properties, without synthesizing and testing the modification. (EX2079, ¶227.)

As shown above, Ascleitis's testing of the two undisclosed compounds also shows that substituting cyclopropyl groups for other moieties of orforglipron does not always lead to desirable properties. (EX2079, ¶228; EX2080, ¶8.) These compounds, in which a cyclopropyl or cyclopropane group was substituted for a methyl group at an additional position on the orforglipron core structure, showed

significantly decreased potency, with one compound completely losing activity. Specifically, the compounds had an EC₅₀ of 1.995 nM or greater than 10 nM (indicating no activity), compared to an EC₅₀ of 0.012 nM for Compound 19. (EX2080, ¶8.) These results show that a skilled artisan could not predict the result of a modification to orforglipron, including the substitution of cyclopropyl groups, without synthesis and testing. (EX2079, ¶229.)

Additionally, small molecule GLP-1R agonists have a history of failing due to poor potency and toxicity. (EX2079, ¶230; EX2046, 4; EX2048; EX2050; EX 2051.) Pfizer, for instance, has discontinued multiple small molecule GLP-1R agonists for safety reasons after early clinical trials. (EX2048; EX2050; EX 2051.) These failures in small molecule GLP-1R agonist development cut against a skilled artisan having a reasonable expectation of success. (EX2079, ¶230.)

Petitioner's total failure to show that a skilled artisan would have a reasonable expectation of success is an yet another reason that Petitioner has failed to show that Compound 19 is obvious. *Eli Lilly & 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).

7. The Objective Evidence Shows that Challenged Compound 19 Was Not Obvious

The objective evidence, including unexpected results and failure of others, further shows that Challenged Compound 19 is not obvious. “Evidence of objective indicia ‘can be the most probative evidence of nonobviousness in the record,’ and objective indicia enable ‘the court to avert the trap of hindsight.’” *Millenium Pharms., Inc. v. Sandoz Inc.*, 862 F.3d 1356, 1368 (Fed. Cir. 2017) (quoting *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358 (Fed. Cir. 2013)). Such is the case here, where the objective evidence further shows that Petitioner’s arguments are infected with hindsight.

Unexpected Results. Compound 19 shows markedly superior potency and pharmacokinetics compared to both orforglipron and Su Compound 175.

Compound 19’s improved potency can be seen in Table 2 of the ’236 Patent, which provides the results of a “biological activity evaluation” of the Challenged Compounds. (EX1001, Table 2; EX2079, ¶316.) Table 2 includes potency (EC₅₀) results for Challenged Compounds 1 and 19, and Ascletis also studied orforglipron in the same assay. (EX2080, ¶¶6-8; EX2079, ¶311.) As shown in the table below, Challenged Compound 19 demonstrates greater than **3- and 7-fold increases** in potency compared to orforglipron and Compound 1 (Su Compound 175), respectively:

Compound 19	Orforglipron	Compound 1
0.012 nm	0.044 nm <i>Over 3-fold less potent</i>	0.094 nm <i>Over 7-fold less potent</i>

(EX1001, Table 2; EX2079, ¶315.) Dr. Pirrung conceded at deposition that increases of this magnitude in potency are “significant” for GLP-1R agonists. (EX2033, 56:4-14; *see also* Pet., 107 (referring to a 1.6-fold increase in potency in Meng as a “significant[] enhance[ment].”).)

Compound 19 also has unexpectedly superior pharmacokinetics as shown in Tables 3 and 4 of the Challenged Patent. Those tables provide C_{max} and/or AUC results for the Challenged Compounds following single dose subcutaneous and oral administrations. (EX1001, 201:31-63, Tables 3-4; EX2079, ¶¶312-313.) Ascletis also calculated other pharmacokinetic parameters for Challenged Compounds 1 and 19 in those studies not shown in the Challenged Patent. (EX2080, ¶¶9-11.) As summarized in the table below, the results of those studies show that Challenged Compound 19 shows far superior pharmacokinetics to orforglipron following both oral and subcutaneous dosing, including a greater than **43-fold improvement** in subcutaneous AUC. (EX2079, ¶318.) Challenged Compounds 19 is also far superior to Challenged Compound (Su Compound 175) for AUC, clearance, and C_{max} following oral dosing. (*Id.*)

	Compound 19	Orforglipron	Compound 1
Single Dose Subcutaneous Injection			
AUC _{0-696h}	234,473 ng*h/mL	5,390 ng*h/mL <i>Over 43-fold worse</i>	60,272 ng*h/mL <i>Nearly 4-fold worse</i>
Cl _F	2.03 mL/min/kg		7.27 mL/min/kg <i>Over 3-fold worse</i>
C _{max}	2603 ng/mL		561 ng/mL <i>Over 4-fold worse</i>
Single Dose Oral Administration			
C _{max}	4,460 ng/mL	799 ng/mL <i>Over 5-fold worse</i>	
AUC _{0-48h}	60,043 ng*h/mL	7,222 ng*h/mL <i>Over 8-fold worse</i>	

While “[m]ere improvement in properties” is not alone enough, “***substantially*** improved results, . . . suffice to establish unexpected results in the absence of evidence to the contrary.” *In re Soni*, 54 F.3d 746, 751 (Fed. Cir. 1995) (emphasis added). As Dr. Wipf explains, the magnitude of improvement in AUC, C_{max} and clearance shown for Challenged Compound 19 is certainly substantial. (EX2079, ¶¶317-318.)

The superior potency and pharmacokinetics of Compound 19 would not have been expected based on the prior art. Nothing in the prior art cited by Petitioner suggests that substituting a cyclopropyl group for the methyl on the indazole moiety of orforglipron and/or removing the dimethyl group on the THP moiety would lead to such significant improvements in potency and pharmacokinetics. (EX2079, ¶325.)

Su contains no data on those substitutions at all. (EX1007.) Yoshino only provides pharmacokinetic data for orforglipron, and its potency data does not suggest that either modification improves potency, much less that the two modifications together would lead to a greater than 3-fold increase in EC_{50} . (EX1008, 311:51-313:34; EX2079, ¶325) Kawai does not include any potency data and only includes pharmacokinetic data for orforglipron. (EX2079, ¶325; EX1004.) And, finally, while Talele suggests generically that cyclopropyl groups can improve metabolic issues for some compounds in some contexts, it has nothing to do with orforglipron and does not suggest the significant improvements in AUC, C_{max} and clearance demonstrated by Challenged Compound 19. (EX1009; EX2079, ¶325.)

Moreover, Ascletis is developing one of the Claimed Compounds, ASC30, which has shown strong promise in early clinical studies. ASC30 has demonstrated promising safety and efficacy data in Phase 1 and 2 clinical trials, including a 6.5% mean reduction in body weight after just 28 days of treatment. (EX2023; EX2022, 2.) ASC30's recent Phase 2 trial also shows that, over a 13-week study, only 22-30% of patients reported vomiting, as well as promising GI tolerability profiles for nausea, diarrhea, and constipation. (EX2042, Table 1; EX2079, ¶326.) ASC30's early success in clinical trials is consistent with the above superior properties.

Further, Ascletis is pursuing ASC30 in both a once-daily oral dosing regimen and a once-monthly subcutaneous dosing regimen. (EX2042, 2.) The superior

potency and pharmacokinetics seen in Challenged Compound 19 likely enable flexibility in dosing regimen. (EX2079, ¶327.) Subcutaneous injection for orforglipron, on the other hand, is not currently being pursued.

Failure of Others. These results are even more remarkable given the failure of others to develop small molecule GLP-1R agonists, which further shows Compound 19 is not obvious. “Evidence that others tried but failed to develop a claimed invention may carry significant weight in an obviousness inquiry.” *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Pat. Litig.*, 676 F.3d 1063, 1081 (Fed. Cir. 2012). In this space, multiple drug companies have failed to develop successful small molecule GLP-1R agonists.

In the 2000s, research labs developed small-molecule GLP-1R agonists but determined the compounds ineligible for further development. (EX2046.) Scientists gave up on one such compound, Boc5, after it was found to have low bioavailability and poor pharmacokinetics and attempts to improve those properties failed. (EX2046, 4.)

In the years since, many companies have attempted to create small molecule GLP-1R agonists. As an example, Pfizer has had three small molecule GLP-1R agonist candidates fail. The first of those drugs, lotiglipron, reached Phase 2 studies before early signs of liver damage forced Pfizer to discontinue the product. (EX2048, 1-2.) The second of those drugs, danuglipron, also showed a likelihood for

hepatotoxicity, causing Pfizer to discontinue the drug. (EX2050, 1.) Pfizer ended research on their third and final small molecule GLP1-R agonist, PF-06954522, just after receiving data from their Phase 1 study. (EX2051.) The failure of Pfizer, a major pharmaceutical company, to develop a small molecule GLP-1R agonist for patients further indicates the nonobviousness of the claimed compounds.

B. Ground 2: Petitioner Fails to Show that Challenged Compounds 1, 19 or 20 Were Obvious Over Yoshino, Kawai, and Talele

Petitioner asserts that claims 1-9, 12-17 and 24-25 are obvious with respect to Compound 1, 19 and 20 in view of Yoshino, Kawai, and Talele. Petitioner's Ground 2 arguments are substantively similar to Ground 1 and, for many of the same reasons, Petitioner has not come close to meeting its burden to show that the Challenged Compounds were obvious.

First, Petitioner has not established any motivation for a skilled artisan to modify orforglipron as needed to achieve Challenged Compounds 1, 19 and 20. More specifically, Petitioner does not articulate any reason that a skilled artisan would seek to modify orforglipron, even generally, much less a reason that would lead to Challenged Compounds 1, 19, or 20. Second, Petitioner has failed to establish that a skilled artisan would have a reasonable expectation of success in achieving those compounds. Third, objective indicia of non-obviousness show that Challenged Compounds 1, 19, and 20 were not obvious.

1. Petitioner Fails to Establish a Motivation to Make the Substitutions Required for the Challenged Compounds

i. Compound 1

Challenged Compound 1 requires the skilled artisan to replace the methyl on the indazole moiety of orforglipron with a cyclopropyl moiety. Petitioner fails to show that a skilled artisan would be motivated to make that substitution to orforglipron.

As discussed above in Section V.A.2, Petitioner fails to identify a “reason that would have led a chemist to modify” orforglipron “in a particular manner.” *Takeda*, 492 F.3d at 1357. Indeed, instead of identifying any property of orforglipron that a skilled artisan would purportedly seek to improve, Petitioner and its expert repeatedly hear praise on orforglipron. (§V.A.2.) Petitioner’s arguments that a skilled artisan would not be *discouraged* from substituting cyclopropyl for the methyl group on the indazole moiety are insufficient. (§V.A.2.)

In addition, for the same reasons articulated above for Ground 1, Petitioner has also failed to show that a skilled artisan would have been motivated to modify orforglipron to replace the methyl on the indazole moiety with a cyclopropyl based on Yoshino, Kawai, and Talele. (§V.A.3.i.) Neither Yoshino, Kawai, or Talele provide the requisite motivation. Moreover, to the extent it argues that Compound 1 is unpatentable as obvious-to-try, Petitioner has failed to meet its burden for the reasons discussed above. (§V.A.5.)

ii. Compound 19

Petitioner has failed to show a skilled artisan would be motivated to make the changes to orforglipron required to achieve Challenged Compound 19 based on Yoshino, Kawai, and Talele for the same reasons discussed in Ground 1. (§V.A.) Petitioner's motivation arguments for Compound 19 are effectively the same for Ground 2 as Ground 1 and fail for the same reasons.

To briefly recap, Petitioner has failed to provide any reason why a skilled artisan would be motivated to modify orforglipron. (§V.A.2.) Moreover, Petitioner has failed to show that a skilled artisan would be motivated to (1) substitute cyclopropyl for the methyl on the indazole moiety in orforglipron or (2) remove both dimethyl groups from the THP moiety, much less (3) make both changes in the same compound. (§V.A.3.) Moreover, to the extent it argues that Compound 19 is unpatentable as obvious-to-try, Petitioner has failed to meet its burden. (§V.A.5.)

iii. Compound 20

Similar to Compound 19, Compound 20 requires three modifications from orforglipron. First, the skilled artisan would have to replace the methyl group on the indazole moiety of orforglipron with a cyclobutyl group. Further, just as in Compound 19, the skilled artisan would have to remove each of the two methyl groups on the THP moiety of orforglipron. Petitioner has failed to demonstrate that a skilled artisan would be motivated to make those changes. For the same reasons

discussed above, Yoshino, Kawai, and Talele would not have motivated a skilled artisan to replace the methyl on the indazole moiety with a cycloalkyl, such as cyclobutyl, and/or to remove the dimethyl group on the THP moiety. (§§V.A.3.i-ii.)

Compound 20 is different than Compound 19 in that it has a cyclobutyl group on the indazole moiety instead of a cyclopropyl group. (EX1001, *compare* Compound 20 *with* Compound 19.) Petitioner does not point to any teaching in Yoshino, Kawai or Talele that would motivate a skilled artisan to substitute a cyclobutyl, in particular, for the methyl group on the indazole moiety. Indeed, Yoshino and Kawai do not disclose any cycloalkyl groups on the indazole moiety, and Talele speaks only to cyclo**propyl** groups (albeit completely outside the context of GLP-1R agonists). (EX2079, ¶255.)

Petitioner states, with no support, that a “four-membered ring cycloalkyl group [is] more resistant to metabolism than simply alkyl groups.” (Pet., 99.) To the contrary, a skilled artisan would have known that cyclobutyl groups can, in fact, make molecules more susceptible to metabolic oxidation and lower potency. (EX2079, ¶256; EX2076, 3-4.) A skilled artisan would also recognize that cyclobutyl rings can be susceptible to ring opening in some circumstances, leading to increased instability. (EX2079, ¶256.) Thus, without a specific reason to think it would lead to desired results, a skilled artisan would not have been motivated to

substitute a cyclobutyl for the methyl group on indazole. (EX2079, ¶258.)
Petitioner's prior art provides no such reason.

Without a specific motivation, a skilled artisan would also have been discouraged from making a cyclobutyl substitution because replacing the methyl group with the cyclobutyl would increase lipophilicity, which lowers the bioavailability of orforglipron. (EX2079, ¶258; EX2072, 6-7 (describing modifications in a potential drug candidate for treatment of immunological diseases, where a more rigid linker, i.e. cyclobutane, increased lipophilicity).) A skilled artisan would not be motivated to modify orforglipron, which is orally administered, to have less bioavailability. (EX2079, ¶258.)

Finally, even if it could show a skilled artisan would be motivated to substitute cyclobutyl for methyl on the indazole moiety, Petitioner does not articulate any motivation for a skilled artisan to make that change *and* remove both methyl groups on the THP moiety in the same compound. Petitioner makes no attempt to explain why a skilled artisan would make both modifications together, and Ground 2 fails as to Compound 20.

2. Petitioner Fails to Establish a Reasonable Expectation of Success of Achieving the Challenged Compounds

Similar to Ground 1, Petitioner fails to provide any analysis or establish a reasonable expectation of success for achieving Challenged Compounds 1, 19, or 20

for Ground 2. Rather, Petitioner merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success in achieving Compound 20 when starting with orforglipron. (Pet., 98-99.) Dr. Pirrung likewise offers no analysis of reasonable expectation of success for Compound 20. (EX1002, ¶¶152-154, 225, 312.)

Petitioner does not identify any particular property of orforglipron that a skilled artisan would seek to improve or any issues with orforglipron. *See Daiichi*, 619 F.3d at 1352; *Institut Pasteur*, 738 F.3d at 1346. Further, Petitioner does not offer any analysis to establish that a skilled artisan would reasonably expect Compounds 1, 19, or 20 to results have desirable properties. And, nothing in Yoshino, Kawai, or Talele suggests that the substitutions required to achieve the Challenged Compounds starting with orforglipron would lead to desirable results. Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compound 20 based on the prior art.

For the same reasons discussed in Section V.A.6, a skilled artisan would not have any reasonable expectation, based on the asserted prior art, that the modifications needed to arrive at Challenged Compound 19 would lead to desirable properties. Those same reasons also apply to Challenged Compounds 1 and 20.

Petitioner's failure to show that a skilled artisan would have a reasonable expectation of success is an yet another reason that Petitioner has failed to show that Compound 20 is obvious. *Eli Lilly*, 8 F.4th at 1344.

3. The Objective Evidence Shows that Challenged Compounds 1, 19 and 20 Were Not Obvious

Objective evidence, including unexpected results and failure of others, shows that Challenged Compounds 1, 19, and 20 are not obvious. *Millenium Pharms.*, 862 F.3d at 1368 (“objective indicia enable ‘the court to avert the trap of hindsight’”).

Unexpected Results. As explained above, Compound 19 demonstrates unexpected superior activity and pharmacokinetics compared to orforglipron. (§V.A.7.)

Challenged Compound 1 also has unexpected, superior properties compared to the closest prior art, orforglipron. Example 3 of the '236 Patent shows that Compound 1 has superior pharmacokinetics to orforglipron. (EX1001, Table 3.) Following a single-dose subcutaneous injection, Compound 1 demonstrated an AUC_{0-696h} of 60,272 ng*h/mL compared to orforglipron's 5,390 ng*h/mL, an ***11-fold increase***. (*Id.*, Table 3.) Such an increase in AUC is significant and can facilitate different dosing regimens, such as monthly injections. (EX2079, ¶¶314, 327.)

Challenged Compound 20 also exhibits superior potency and pharmacokinetics over orforglipron. Table 2 includes potency (EC₅₀) results for

Challenged Compound 20, and Ascletis also studied orforglipron in the same assay. (EX1001, Table 2; EX2080, ¶¶6-8; EX2079, ¶311.) As shown below, Compound 20 showed an increase of potency greater than 2.4-fold compared to orforglipron.

Compound 20	Orforglipron
0.018 nm <i>Over 2.4-fold greater</i>	0.044 nm

Dr. Pirrung conceded at deposition that increases of this magnitude in potency are “significant[]” for GLP-1R agonists. (EX2033, 56:4-14; *see also* Pet., 107 (referring to a 1.6-fold increase in potency in Meng as a “significant[] enhance[ment].”).)

Compound 20 also demonstrates superior pharmacokinetic properties compared to the closest prior art. In the '236 Patent's subcutaneous dose study, Compound 20 demonstrated an AUC_{0-696h} that exceeded orforglipron by ***over 14-fold***, evidencing superior subcutaneous pharmacokinetics. (EX 1001, Table 3.) In the oral dose study, Compound 20 exhibited a C_{max} and AUC_{0-48h} both more than 2-fold greater than orforglipron's. (*Id.*, 201:31-202:50, Table 4.)

	Compound 20	Orforglipron
Single Dose Subcutaneous Injection		
AUC _{0-696h} , ng*h/mL	77,688 ng*h/mL <i>Over 14-fold greater</i>	5,390 ng*h/mL
Single Dose Oral Administration		
C _{max} , ng/mL	1,900 ng/mL <i>Over 2-fold greater</i>	799 ng/mL
AUC _{0-48h} , ng*h/mL	16,982 ng*h/mL <i>Over 2-fold greater</i>	7,222 ng*h/mL

(EX1001, 201:31-63, Tables 3-4.) Compound 20's pharmacokinetics and potency are thus both superior properties to the closest prior art. (EX2079, ¶¶320-322.)

Nothing in the prior art cited by Petitioner suggests that the substitutions required to achieve Compounds 1, 19 and 20 from orforglipron would lead to the improved potency and pharmacokinetic results described above. The prior art cited does not suggest that substituting a cycloalkyl group for the methyl on the indazole moiety of orforglipron and/or removing the dimethyl group on the THP moiety would lead to such significant improvements in potency and pharmacokinetics. (EX2079, ¶325.) Yoshino's potency data does not suggest that either modification improves potency, or that both modifications together would lead to a greater than 3-fold increase in EC₅₀. (EX1008, 311:51-313:34; EX2079, ¶325.) Yoshino and Kawai do not provide pharmacokinetic data for any compound other than orforglipron. (*Id.*; EX1008; EX1004.) Yoshino's potency data does not suggest that

either modification improves potency, or that both modifications together would lead to a greater than 3-fold increase in EC₅₀. (EX1008, 311:51-313:34; EX2079, ¶325.) And while Talele suggests that cyclopropyl groups can improve metabolic issues for some compounds in some contexts, it has nothing to do with orforglipron and does not suggest the superior pharmacokinetics or potency demonstrated by Challenged Compounds 1, 19 and 20. (EX1009.)

Further, as explained in the context of Ground 1, one of the Claimed Compounds (ASC30) has also shown promising efficacy in Phase 1 and 2 studies, consistent with the superior properties demonstrated in the '236 Patent. (See §V.A.7.) The improved potency and pharmacokinetics of the Challenged Compounds likely enables Ascletis to pursue flexible dosing for ASC30. (See §V.A.7.)

Failure of Others. The failure of others to create small molecule GLP-1R agonists also shows that Compounds 1, 19, and 20 are not obvious. *In re Cyclobenzaprine*, 676 F.3d at 1081. As discussed above for Ground 1, multiple drug companies have tried and failed to develop oral small molecule GLP-1R agonists. (§V.A.7.) For instance, Pfizer has had three different GLP-1R agonists fail in clinic. (See §V.A.7.) These failures further show that Compounds 1, 19, and 20 were far from obvious.

C. Ground 3: Petitioner Fails to Show that Claimed Compound 65 Was Obvious

In Ground 3, Petitioner opines that Compound 65 is obvious over a combination of Su, Yoshino, Kawai, Talele, Meng, Patel and/or Ren.⁹ (Pet., 106.) Relying on Grounds 1 and 2, Petitioner begins its Ground 3 analysis with Compound 19. (Pet., 106) Compound 19, however, is not in the prior art, nor obvious, for the reasons discussed in Grounds 1 and 2. (§§V.A.-B.) Ground 3 fails for this reason alone.

As explained below, Petitioner also fails to establish that a skilled artisan would have been motivated to make all of modifications to orforglipron (or Su Compounds 44 or 175) required to achieve Compound 65. Moreover, Petitioner does not even address expectation of success, and the prior art does not establish that a skilled artisan would have had any such expectation of achieving Compound 65. The objective evidence further confirms Compound 65 is not obvious.

⁹ Petition’s Identification of Challenge section states that Ground 3 includes the Ground 1 references plus Meng, Patel and Ren. (Pet., 7.) In Ground 3, however, Petitioner identifies “the combination of Su, Yoshino, and Kawai, further in view of Talele, Patel, and Pennington.” (Pet., 105.) Petitioner has not properly alleged an unpatentability challenge to the extent Petitioner asserts Pennington in Ground 3, and should not be able to argue it on Reply. 37 C.F.R. §42.204(b)(4); *Intelligent Bio-Sys, Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1369-70 (Fed. Cir. 2016).

1. Ground 3 Depends on Grounds 1 or 2 and Fails for the Same Reasons

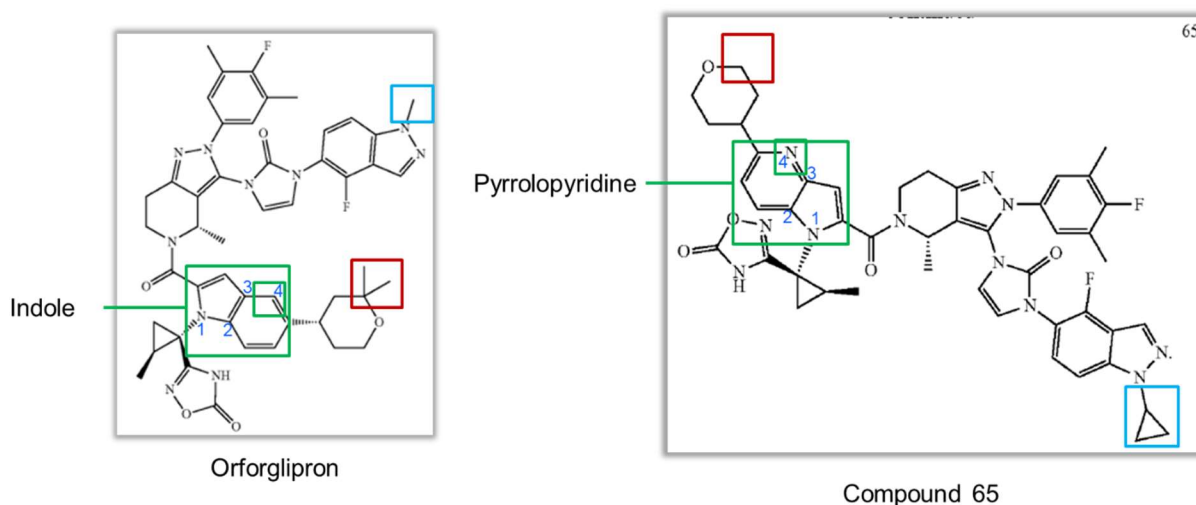
Petitioner relies on the analysis in Grounds 1 and 2 to arrive at Compound 19 and then relies on Meng, Patel, and Ren solely to support its argument that a skilled artisan would substitute a nitrogen atom on the at a specific position of the orforglipron ring structure. (Pet., 106-112.) Petitioner’s analysis in Ground 3 therefore depends on the success of Grounds 1 and 2. As explained above, however, Grounds 1 and 2 both fail because Petitioner fails to show that Su, Yoshino, Kawai, and/or Talele provide any motivation to make Compound 19 or that a skilled artisan would have a reasonable expectation of success. (§§V.A-B.) Thus, a skilled artisan would not “build[] upon the structure of Compound 19” to make Compound 65 because the prior art does not disclose or render Compound 19 obvious in the first place. (Pet., 106.)

Further, Petitioner’s starting point of Compound 19 itself is improper hindsight, as Petitioner assumes that a skilled artisan would first arrive at Compound 19 and then further modify Compound 19 to arrive at Compound 65, using the challenged patent as a guide. *Otsuka Pharm.*, 678 F.3d at 1296 (“The inventor’s own path itself never leads to a conclusion of obviousness; that is hindsight.”); *Sensonics, Inc. v. Aerosonic Corp.*, 81 F.3d 1566, 1570 (Fed. Cir. 1996) (“The invention must

be viewed not after the blueprint has been drawn by the inventor. . . .”) (citing *Interconnect Planning Corp. v. Feil*, 774 F.2d 1132, 1138 (Fed. Cir. 1985)).

2. Petitioner Fails to Show a Motivation to Make the Changes Needed to Arrive at Compound 65

Compound 65 has multiple modifications compared to orforglipron, as depicted below in the green, red, and blue boxes.



As shown above in the green boxes, Compound 65 includes a nitrogen atom at the 4-position on the indole moiety of orforglipron, resulting in a pyrrolopyridine. (EX2079, ¶274.)

Petitioner does not show that a skilled artisan would have been motivated to replace the carbon at the 4-position of the indole moiety with a nitrogen atom. Petitioner relies on Meng, Patel, and Ren for this substitution, but none of those references would motivate a skilled artisan to replace the relevant carbon atom on the indole moiety of orforglipron with a nitrogen. (Pet., 106-112.)

As an initial matter, as with its other arguments, Petitioner does not identify any characteristic of orforglipron that a skilled artisan would seek to change or improve. As Dr. Wipf explains, a skilled artisan would not seek to modify a compound such as orforglipron without defining the target compound profile (“TCP”) or identifying a property of orforglipron to be improved. (EX2079, ¶276.) Petitioner does not identify any particular criteria or goal for modifying orforglipron. *Amerigen Pharms.*, 913 F.3d at 1089 (“A general motivation to modify [the lead compound] based on a prior patent would not suffice[.]”).

Absent a specific motivation to do so, a skilled artisan also would not have been motivated to introduce a nitrogen atom on the indole moiety for at least two reasons. First, a skilled artisan would know that substituting a nitrogen atom in the benzene ring often leads to decreased activity in compounds. For instance, replacing a carbon in a benzene ring with a nitrogen, as in Compound 65, can lead to decreased biological activity or increases in metabolic degradation. (EX2078, 6, Table 1.) Second, a skilled artisan would understand that substituting the carbon atom for a nitrogen atom would be synthetically more challenging. (EX2052, 1-2 (“[c]ompared to indoles, however, [pyrrolopyridines] are far more challenging to prepare, especially in highly functionalized form.”).) Thus, without any particular motivation to improve or change any property of orforglipron, a skilled artisan would be

discouraged from introducing a nitrogen on the indole to form a pyrrolopyridine.
(EX2079, ¶277.)

A skilled artisan would also understand that there could be a number of different substitutions possible on indole moieties. “A typical lead optimization program often involves a trial-and-error process of replacing chemical functionality, including rings, and in most cases this intellectual exercise is based on a chemist’s knowledge and recollection of his or her past experience.” (EX2034, 47) Petitioner’s focus solely on modifying the carbon at the 4-position of the indole moiety with a nitrogen is pure hindsight and guided by the challenged patent, not the prior art. *Otsuka Pharm.*, 678 F.3d at 1296.

Meng. Turning to Petitioner’s prior art, Meng does not provide the requisite motivation for a skilled artisan to make the required nitrogen substitution.

Petitioner’s selection of Meng is more cherry-picking. Meng is just one of numerous patent documents that disclose potential modifications to the core structure of orforglipron. (EX1029, [0007]-[0019]; EX2079, ¶279.) Petitioner provides no reason why a skilled artisan would select Meng from the sea of orforglipron-related prior art. *WBIP, LLC v. Kohler Co.*, 829 F.3d 1317, 1337 (Fed. Cir. 2016) (“The real question [on obviousness] is whether that skilled artisan would have plucked one reference out of the sea of prior art.”).

Petitioner's selection of Compound (II) in Meng is yet more cherry-picking. Meng discloses a generic structure for a GLP-1 receptor agonist that encompasses thousands of potential structures. (EX1029, [0007]; EX2079, ¶279.) Despite this broad disclosure, Petitioner relies exclusively on Meng Compound (II), which incorporates a nitrogen atom on the indole moiety in the same location as Compound 65. (EX2079, ¶280; EX1002, ¶275.) Without explanation, Petitioner ignores Meng Compound (III), which Meng shows is more potent than Compound (II). (Pet., 106-107; EX2033, 57:2-6; EX1029, [0186]-[0192]; EX2079, ¶281.) If anything, a skilled artisan looking at Meng would focus on the compound with better activity, Compound (III). *Otsuka Pharm.*, 678 F.3d at 1292-93 (“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 nonetheless focuses on Compound (II) because it substitutes the nitrogen atom in the same position on the indole moiety as Compound 65, whereas Compound (III) does not. (Pet., 106-107; EX2033, 57:20-58:6.) The only reason for doing so is impermissible hindsight. *Otsuka Pharm.*, 678 F.3d at 1296 (explaining that an obviousness conclusion may not be derived based on hindsight from “[t]he inventor’s own path”).

Patel. Patel also would not motivate a skilled artisan to substitute a nitrogen on the benzene ring of the indole in orforglipron.

Patel is a general review article that discusses the use of pyridines, generally, in medicinal chemistry. (Pet., 108-109.) Patel is not directed to GLP-1R agonists, and Petitioner does not explain why a skilled artisan would look to Patel in the first place. (EX1026.) Additionally, Patel is one of many review articles that generally discuss different functional ring groups used in medicinal chemistry. (EX2079, ¶284.) For example, other articles discuss the potential benefits of pyridines, piperidines, piperazines, pyrimidines, pyrazoles, triazoles, imidazoles, and fused and monocyclic heterocycles. (EX2053-EX2064.) A skilled artisan would be just as likely to consider any of these scaffolds for substitution purposes as Patel. (EX2079, ¶284.) Petitioner provides no reason why a skilled artisan would focus on Patel and ignore all of these other potential changes to the orforglipron ring structure.¹⁰

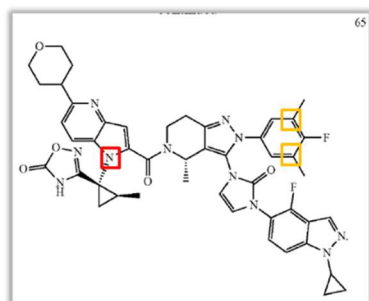
Even considering it, Patel does not focus on substituting a nitrogen for a carbon in any particular position of an indole moiety, much less suggest the specific substitution in Compound 65. (EX2079, ¶283.) Therefore, Patel cannot possibly provide the motivation to make the specific substitution at carbon 4 in the indole moiety of orforglipron. (*Id.*)

¹⁰ To the extent Petitioner relies on it, Pennington is also a generic article not directed to GLP-1R agonists and would not motivate a skilled artisan to substitute a nitrogen at the same position as Challenged Compound 65. (EX2079, ¶284.)

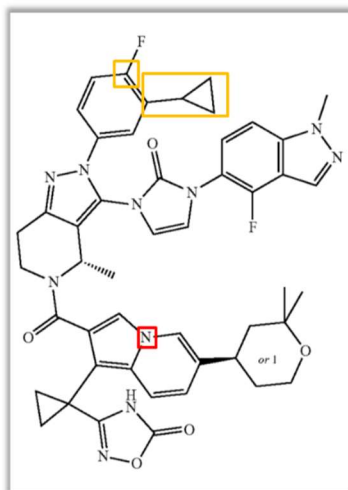
Ren. Ren likewise would not have motivated a skilled artisan to make a nitrogen substitution at carbon 4 of the indole moiety.

Petitioner relies on two compounds in Ren (Compounds 76 and 90) that do not even make the same substitution as Claimed Compound 65. (Pet., 110-112.) Rens's Compound 76 incorporates a nitrogen atom in a different position than Compound 65, (EX1002, ¶281; EX2079, ¶286), and Ren's Compound 90 includes *two* nitrogen substitutions on the indole moiety, (EX1002, ¶¶281-282; EX2079, ¶286). Thus, even if Ren encouraged a skilled artisan to make the substitutions in its Compounds 76 and 90, those substitutions would not lead to Claimed Compound 65. (EX2079, ¶286.)

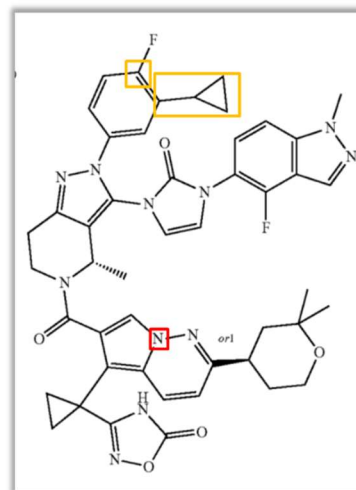
Compounds 76 and 90 also have other modifications not seen in the Challenged Compounds (annotated in yellow boxes below).



Compound 65



Compound 76
(Ren)



Compound 90
(Ren)

Petitioner focuses only on the nitrogen substitutions in Compounds 76 and 90 without any explanation why, if they were interested in these compounds, a skilled artisan would make the substitution on the indole moiety but not also the substitution on the fluorophenyl ring. (Pet., 110-112.) Petitioner's focus on solely the nitrogen substitution on one position in the compounds in Ren to the exclusion of the other modifications further highlights the hindsight-based nature of the Petition.

A skilled artisan, if considering Ren, would in fact focus on Ren Compound 73, instead of Compounds 76 and 90, based on the disclosed pharmacokinetic data. The pharmacokinetic data disclosed in Ren shows that Compound 73 has a better bioavailability compared to Compounds 76 and 90. (EX2079, ¶289; EX1030, 459:60-460:10.) Petitioner's expert points to Table 30 in Ren to support his opinion that a skilled artisan would have incorporated a nitrogen atom in the indole moiety based on the data disclosed for Compound 90, which is better than the data disclosed for Compound 76. (EX1002, ¶¶282-283.) Compound 73, however, has a higher C_{max} and AUC than both Compounds 90 and 76, and its oral bioavailability, F, is 90% compared to 59% for Compound 90 and 30% for Compound 76.

TABLE 30-continued

Cmpd No.	Dose (mg/kg)	PO parameters		
		C_{max} (ng/mL)	AUC (ng hr/mL)	F (%)
73	5	1700	10193	90
76	5	962	5321	30
90	5	1370	3338	59
91	5	738	2661	22

(EX2079, ¶289; EX1030, Table 30 (annotated).) If anything, a skilled artisan would therefore focus on Compound 73 (which does not have a nitrogen atom at the relevant position) over Compound 90. (EX2079, ¶290.)

No motivation to make all needed changes. Finally, even if a skilled artisan would be motivated to make the very specific modification to the orforglipron ring structure in Compound 65, Petitioner fails to explain why they would also be motivated to make *all the modifications* needed to achieve Compound 65 starting with orforglipron (or Su's compounds). There is simply nothing in the prior art that suggests substituting the methyl group on the indazole moiety for a cyclopropyl, removing the dimethyl group on the THP ring, and making a nitrogen substitution in the indole moiety, all in the same compound. (EX2079, ¶291.) A skilled artisan would have understood that a compound's biological activity results from the structure as whole and individual modifications do not lead to a predictable result when made together. (*Id.*) Thus, a skilled artisan would have no reason to think that all of these modifications, if made in the same compound, would lead to a desirable result. (*Id.*)

3. Petitioner Fails to Establish a Reasonable Expectation of Success in Achieving Compound 65

Similar to Compounds 1, 19, and 20, Petitioner fails to provide any analysis or establish a reasonable expectation of success for achieving Compound 65. Rather,

Petitioner merely states in conclusory manner that the prior art would give a skilled artisan a reasonable expectation of success in achieving Compound 65 when starting with orforglipron. (Pet., 111.) Dr. Pirrung likewise offers no analysis of reasonable expectation of success for Compound 65. (EX1002, ¶¶152-154, 225, 312.)

Petitioner does not identify any particular property of orforglipron that a skilled artisan would seek to improve or any issues with orforglipron. *See Daiichi*, 619 F.3d at 1352; *Institut Pasteur*, 738 F.3d at 1346. Further, Petitioner does not offer any analysis to establish that a skilled artisan would reasonably expect the modifications required by the Compound 65 to actually result in whatever (unidentified) properties a skilled artisan would purportedly seek in modifying orforglipron. And, nothing in the asserted prior art suggests that changes needed to achieve Challenged Compound 65 would lead to desirable results. Thus, a skilled artisan would not have a reasonable expectation of success in achieving Compound 65 based on the prior art.

A skilled artisan would also know that modifying the ring structure of orforglipron is a complex process that would require considering of the properties of the different ring moieties and testing each one to determine how it affects the properties of the overall drug compound. (EX2079, ¶294.) Thus, any effort to make substitutions to the orforglipron ring structure would be a trial-and-error process to determine the effect of each substitution, and a skilled artisan would not have a

reasonable expectation of success in achieving Compound 65 based on the prior art.
(EX2079, ¶295.)

In addition, for the same reasons discussed in Section V.A.6, the prior art did not provide a reasonable expectation that the modifications needed to arrive at Challenged Compound 65 would lead to desirable properties.

Petitioner's total failure to show that a skilled artisan would have a reasonable expectation of success is yet another reason that Petitioner has failed to show that Compound 65 is obvious. *Eli Lilly*, 8 F.4th at 1344.

4. The Objective Evidence Shows that Challenged Compound 65 Was Not Obvious

The objective evidence, including unexpected results and failure of others, further shows that Challenged Compound 65 is not obvious. *Millenium Pharms.*, 862 F.3d at 1368 (“objective indicia enable ‘the court to avert the trap of hindsight.’”).

Unexpected Results. Compound 65 unexpectedly demonstrates superior properties to both orforglipron and Challenged Compound 1 (Su Compound 175).

Compound 65, first, has superior pharmacokinetics compared to orforglipron. As shown in Table 4 of the '236 Patent, following a single-dose oral administration, Compound 65 demonstrated a C_{max} more than **13-fold** orforglipron's and an AUC_{0-48h} more than **10-fold** that of orforglipron. (EX2079, ¶323; EX1001, 201:31-202:50,

Table 4.) Such an increase in pharmacokinetics is significant and can facilitate different dosing regimens, such as monthly injections. (EX2079, ¶327.)

Compound 65 also showed a significant increase in solubility compared to Challenged Compound 1 (Su Compound 175). (EX2079, ¶324.) Ascletis's experiments show that Challenged Compound 1 has a solubility of 0.0587 mg/mL at pH 11, compared to 6.650 mg/mL for Challenged Compound 65. (EX2081; EX2079, ¶324; EX2080.) That increase of *over 100-fold in solubility* is significant and may offer advantages for pharmaceutical development of Compound 65 over Compound 1. (EX2079, ¶324.)

Nothing in the prior art cited by Petitioner suggests that the substitutions required to achieve Compounds 65 would lead to the improved pharmacokinetic and solubility results described above. Su only discloses pharmacokinetic data for five compounds, none of which have the substitutions required by Compound 65. (EX2079, ¶325; EX1007.) Yoshino and Kawai do not provide pharmacokinetic data for any compound other than orforglipron. (EX2079, ¶325; EX1008; EX1004.) And while Talele suggests that cyclopropyl groups can improve metabolic issues for some compounds in some contexts, it has nothing to do with orforglipron and does not suggest the superior pharmacokinetics demonstrated by Challenged Compound 65. (EX1009.) None of Meng, Patel or Ren provide pharmacokinetic data for compounds with the modifications of Compound 65. (EX2079, ¶325.) Moreover,

none of the prior art teaches improvements in solubility, much less the 100-plus fold increase in solubility seen in Compound 65.

As explained in the context of Compound 19, one of the Claimed Compounds (ASC30) has also shown promising efficacy in Phase 1 and 2 studies, consistent with the superior properties demonstrated by the Challenged Compounds. (*See* §V.A.7.) Further, Ascletis is pursuing ASC30 in both a once-daily oral dosing regimen and a once-monthly subcutaneous dosing regimen, likely due to the superior potency and pharmacokinetics seen in the Challenged Compounds. (§V.A.7.).

Failure of Others. The failure of others to create small molecule GLP-1R agonists also shows that Compound 19 is not obvious. *In re Cyclobenzaprine*, 676 F.3d at 1081. As discussed above for Ground 1, multiple drug companies have tried and failed to develop oral small molecule GLP-1R agonists. (§V.A.7.) For instance, Pfizer has had three different GLP-1R agonists fail in clinic. (*See* §V.A.7.) These failures further show that Compounds 1, 19 and 20 were far from obvious.

D. Grounds 1-3: Petitioner Further Fails to Show that the Salts of Claims 2-4, 8-9, 13-14, 16-17, and 22-23 Are Obvious

Claims 2-4, 8-9, 13-14, 16-17, and 22-23 claim certain salts of Challenged Compounds 1, 19, 20, and/or 65. These claims are all non-obvious because Challenged Compounds 1, 19, 20, and 65 are not obvious. (§V.A-C.) In addition,

Petitioner has not established a sufficient motivation or an expectation of success in achieving the claimed salts.

Petitioner relies preliminary on Yoshino, but that reference does not establish a motivation to try to make the salts of the Challenged Compounds. Yoshino merely discloses a list of *potential counterions* that a skilled artisan could consider trying to form a salt with *the many compounds disclosed in Yoshino*. (EX1008, 34:8-14; EX2079, ¶298.) Yoshino does not disclose if the inventors successfully made any actual salts of the Yoshino compounds. (EX1008; EX2079, ¶298.) A skilled artisan would know that salts are unpredictable, and even molecules that are close analogs of each other may not form salts with the same counterions. (EX2079, ¶300.) Thus, even if Yoshino disclosed successful salts of its compounds, which it does not, a skilled artisan would not necessarily be motivated to attempt the same salts of even a structurally similar compound. (EX2079, ¶301.)

Yoshino also does not demonstrate a reasonable expectation of success for making the claimed salts. A skilled artisan would understand that salts are unpredictable, and that there is no way of knowing whether a particular compound will form a salt with a particular counterion in advance. (EX2079, ¶299.) The only way for a skilled artisan to determine whether a particular salt will form is to conduct a salt screen with that particular compound. (EX2079, ¶299.) Further, different salts can show dramatically different properties, including solubility, stability,

hygroscopicity, bioavailability, toxicity, polymorphism, and ease of manufacture. (EX2073.) And even minor structural changes in the compound can alter the coordination geometry of a salt, stoichiometry, and solid-state behavior. (EX2075, Abstract.) Thus, a skilled artisan would know that salts are unpredictable and even molecules that are close analogs of each other as salts could have significantly different properties.

Further, Petitioner cannot rely on Dr. Pirrung to establish that the claimed salts are obvious. Dr. Pirrung admitted at deposition that he has never been involved in the discovery of salts of small molecules and does not know what properties a skilled artisan would look for when determining whether a particular salt is a good candidate for further development. (EX2033, 19:14-25:18.) Dr. Pirrung's testimony should thus be given no weight on this issue. *Chevron Oronite*, No. IPR2018-00922, *aff'd*, 2022 WL 3147683.

Thus, for these additional reasons, Petitioner has not shown that Claims 2-4, 8-9, 13-14, 16-17, and 22-23 are obvious.

E. Ground 4: Petitioner Fails to Show that the Hemi-Calcium Salt of Compound 1 (Claims 4 And 9) Was Obvious

Claims 4 and 9 claim a hemicalcium salt of Compounds 1, 13, 18, 19, 20, 21, and 65 and a hemicalcium salt of Compound 1, respectively. In Ground 4, Petitioner asserts that Challenged Claims 4 and 9 are obvious over Su and Bethel.

Petitioner, first, offers no reason that a skilled artisan would select Su's Compound 175 to make a hemicalcium salt. To the contrary, as explained in detail above, a skilled artisan would have no reason to pick Su out of the sea of orforglipron prior art or select Su's Compound 175 as a lead compound. (§V.A.1.) Thus, a skilled artisan would not select Compound 175 as a lead compound for further development.

Even starting with Su Compound 175, the prior art would not motivate a skilled artisan to try to make its hemicalcium salt. Su does not disclose any salts of Compound 175. And Bethel only discloses a hemicalcium salt of orforglipron. Neither reference teaches or suggests to a skilled artisan to make a hemicalcium salt of Su Compound 175.

A skilled artisan would also have known that salt selection is unpredictable, and that a screening process would be necessary to identify an optimal salt. (EX2070.) There are a large number of potential counterions and hundreds of solvents and solvent mixtures a skilled artisan must choose from to try to form a salt, each of which is tested individually to determine if a salt can be formed. (EX2079, ¶306.) A skilled artisan would not focus on a single counter-ion, even if it formed a salt with a structurally similar compound. (EX2079, ¶307.)

A skilled artisan would not be motivated to form a hemicalcium salt of the claimed compounds based on the disclosures in Bethel. (EX2079, ¶308.) Petitioner provides no explanation why a skilled artisan would choose to make a hemicalcium

salt based on the disclosure in Bethel. Indeed, there is nothing in Bethel that suggests that the hemicalcium salt of orforglipron is better or has improved properties compared to any other salt of orforglipron. (EX1032; EX2079, ¶308.) Bethel does not disclose any stability data or other properties of the hemicalcium salt of orforglipron that would lead a skilled artisan to select a hemicalcium salt for a different compound. (EX1032; EX2079, ¶308.) Thus, a skilled artisan would have no reason to try to make a hemicalcium salt of the claimed compounds based on Bethel. (EX2079, ¶308.)

Petitioner also fails to establish a reasonable expectation of success of making a hemicalcium salt of Challenged Compound 1. A skilled artisan would understand the unpredictability of salt formation. (EX2079, ¶307.) As explained above, there is no way for a skilled artisan to be able to predict whether any particular compound and counterion will form a salt. (EX2079, ¶307.) Moreover, each compound has different properties, resulting in different salts. (EX2079, ¶307; EX2070, Abstract.) Thus, a skilled artisan would therefore not be able to reasonably predict which salts will form, even for compounds that are structural analogs of each other.

Finally, as discussed in more detail above, Dr. Pirrung's has never been involved in the discovery of salts of small molecules (EX2033, 19:14-25:18), and his testimony should thus be given no weight on this issue. *Chevron Oronite*, No. IPR2018-00922, *aff'd*, 2022 WL 3147683.

VI. CONCLUSION

Petitioner has failed to meet its burden of establishing unpatentability of the challenged claims of the '236 Patent, at least for the reasons set forth above.

Dated: March 5, 2026

Respectfully submitted,

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

This **Patent Owner's Response** complies with the type-volume limitation of 18,700 words, comprising 18,684 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: March 5, 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 5th day of March 2026, the foregoing **PATENT OWNER'S RESPONSE** was served electronically via email on the following:

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