

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

**PETITIONER'S RESPONSE TO PATENT OWNER'S
REQUEST FOR DISCRETIONARY DENIAL OF INSTITUTION**

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PETITIONER’S EXHIBIT LIST

Exhibit No.	Description
EX1001	U.S. Patent No. 12,234,236 (“the ’236 Patent”)
EX1002	Declaration of Michael C. Pirrung, Ph.D.
EX1003	Excerpts of File History of U.S. Patent No. 12,234,236
EX1004	Kawai, <i>et al.</i> , Proc Natl Acad Sci U S A., 117(47):29959-29967 (2020) (“Kawai”)
EX1005	International Publication No. WO 2025/026270A1 (“Su”)
EX1006	Chinese Patent Application No. 202311372605.9 (“Su II”), which is a priority document of Su
EX1007	Certified English Translation of Chinese Patent Application No. 202311372605.9 (“Su II”)
EX1008	U.S. Patent No. 10,858,356 to Yoshino, et al (“Yoshino”)
EX1009	Talele, Journal of Medicinal Chemistry, 59(19):8712–8756 (2016) (“Talele”)
EX1010	Liu, <i>et al.</i> , Expert Opinion on Therapeutic Patents, 30(10):781-794 (2020)
EX1011	Pratt, <i>et al.</i> , Diabetes Obes Metab., 25(9):2642-2649 (2023)
EX1012	Frias, <i>et al.</i> , Lancet, 402(10400):472–483 (2023)
EX1013	Chinese Patent Application No. 202311371725 (“the ’725 Provisional”)
EX1014	Certified English Translation of Chinese Patent Application No. 202311371725
EX1015	Chinese Patent Application No. 202311189557 (“the ’557 Provisional”)

Exhibit No.	Description
EX1016	Certified English Translation of Chinese Patent Application No. 202311189557
EX1017	U.S. Patent Provisional Application No. US 63/538,892 (“the ’892 Provisional”)
EX1018	Chinese Patent Application No. 202410142451 (“the ’451 Provisional”)
EX1019	Certified English Translation of Chinese Patent Application No. 202410142451 (“the ’451 Provisional”)
EX1020	Chinese Patent Application No. 202311582240 (“the ’240 Provisional”)
EX1021	Certified English Translation of Chinese Patent Application No. 202311582240
EX1022	Chinese Patent Application No. 202311686034 (“the ’034 Provisional”)
EX1023	Certified English Translation of Chinese Patent Application No. 202311686034
EX1024	U.S. Patent Provisional Application No. 63/545,615 (“the ’615 Provisional”)
EX1025	U.S. Patent Provisional Application No. 63/603,854 (“the ’854 Provisional”)
EX1026	Patel & Burns, J Am Chem Soc., 144(39):17797-17802 (2022) (“Patel”)
EX1027	Pennington & Moustakas, J Med Chem., 60(9):3552-3579 (2017)
EX1028	Chinese Patent Publication No. CN117069743A (“Meng”)
EX1029	Certified English Translation of Chinese Patent Publication No. CN117069743A

Exhibit No.	Description
EX1030	U.S. Patent No. 12,037,339 (“Ren”)
EX1031	Certified English Translation of International Publication No. WO 2025/026270A1 (“Su”)
EX1032	International Publication No. WO 2024/129676A1 (“Bethel”)
EX1033	International Publication No. WO 2024/169952A1 (“Huang”)

I. INTRODUCTION

Patent Owner’s discretionary denial brief (Paper 9, herein “DDB”) tacitly concedes that nearly every consideration from the Acting Director’s March 26, 2025 Memorandum (“Director’s Memo”) weighs in favor of *not* exercising discretionary denial. Indeed, Patent Owner ignores that petitions for post-grant review (“PGRs”) are favored because their early review is close in time to examination and before any settled expectations. Moreover, there is no concern with duplication of costs or efforts since there is no concurrent adjudication of the ’236 Patent. Patent Owner’s only arguments—that *Advanced Bionics* and Petitioner’s patent application warrant an exercise of discretionary denial—ignores the law, the facts, and common sense.

Petitioner explained why the asserted art was not considered by the Examiner and why the Examiner erred. The Examiner conducted a late night prior art search on October 28, 2024—listing hundreds of compounds, signed the Statement of Reasons for Allowance *the next day*, received hundreds of references from Patent Owner a few days later, and then formally issued a Notice of Allowance (NoA) just two business days after that. (EX1003, 169 (showing signature on 10/29/2024), 176-703 (report run 10/28/24), 704-812 (IDS).) The NoA cited only a single compound copied from the search report, not from Patent Owner’s submissions. (*Id.* 168-169.) Thus, the Examiner made his/her decision on patentability before Patent Owner’s references were submitted. Patent Owner’s assertion that the Examiner reviewed and

meaningfully considered each of these references lacks credibility.

Regardless, the Petition explains why other art was never before the Examiner and is not cumulative and why the asserted art and grounds would readily suggest using and modifying certain lead compounds not expressly considered by the Examiner. The Petition presents (i) specific combinations of references not previously considered, (ii) detailed mapping to *all* claim elements with particularized motivations to combine, and (iii) expert testimony explaining why a POSA would have arrived at the claimed compounds with a reasonable expectation of success. That is precisely the kind of enhanced record that the Board has found sufficient to proceed despite prosecution history.

In short, Patent Owner's brief substitutes invective for substance and misstates both the prior art landscape and the § 325(d) standard. The Petition presents an evidence-backed obviousness case that the Office has not meaningfully addressed, which warrants a denial of Patent Owner's DDB.

II. STANDARD FOR DISCRETIONARY DENIAL UNDER § 325(D)

Petitions for PGR are favored because they must be filed no later than nine months from the grant of the patent (35 U.S.C. § 321(c)), are close in time to examination, and occur before expectations in the patent rights are strongly settled. *LifeVac, LLC v. DCSTAR Inc.*, IPR2025-00454, Paper 11 at 2 (Director July 11, 2025). The Board considers whether the same or substantially the same prior art or

arguments were previously before the Office during prosecution. 35 U.S.C. § 325(d); *Advanced Bionics, LLC v. Med-El Elektromedizinische Gerate GMBH*, IPR2019-01469, Paper 6 at 7-8 (PTAB Feb. 13, 2020) (precedential). In making this consideration, the Board uses a two-part test: (1) whether the same or substantially the same art or arguments were previously presented to the Office; and, if the first part is met, (2) whether the petitioner has shown that the Office erred in a material way with respect to patentability. *Id.* at 8.

In the Director's Memo, the PTAB outlined a non-exhaustive list of relevant considerations for discretionary denial including: (1) whether the PTAB or another forum has already adjudicated the validity or patentability of the challenged patent claims; (2) whether there have been changes in the law or new judicial precedent issued since issuance of the claims that may affect patentability; (3) the strength of the unpatentability challenge; (4) the extent of the petition's reliance on expert testimony; (5) settled expectations of the parties, such as the length of time the claims have been in force; (6) compelling economic, public health, or national security interests; and (7) any other considerations bearing on the Director's discretion.

III. ARGUMENT

Patent Owner's DDB disregards both the relevant factors in the Director's Memo and the Director's guidance favoring PGR petitions. Here, there are no settled expectations; there is no concurrent litigation pending; Patent Owner dumped

hundreds of references on the Examiner just two business days before allowance; and Petitioner has set forth a strong unpatentability case—which does not run afoul of *Advanced Bionics*. For these reasons, and because there is no dispute the other considerations from the Director’s Memo do not support discretionary denial, the Director should decline to exercise discretion here.

A. No Settled Expectations

Patent Owner has no, nor argues any, settled expectations. (*See generally* Paper 9.) Indeed, PGR petitions are favored precisely because they must be filed within nine months of issuance, “before expectations in the patent rights are strongly settled.” *LifeVac*, IPR2025-00454, Paper 11 at 2. “Early challenges favor robust, predictable rights and weigh against discretionary denial.” *Intas Pharma. Ltd. v. Atossa Therapeutics, Inc.*, PGR2025-00043, Paper 12 at 2 (PTAB Aug. 29, 2025).

Here, the challenged patent was issued on February 25, 2025, and Petitioner filed this PGR less than four months later, on June 20, 2025. (*Compare* EX1001 with Paper 1.) Thus, there are no settled expectations and Patent Owner’s request should be denied. *See, e.g., Intas Pharma.*, PGR2025-00043, Paper 12 at 2 (rejecting discretionary denial where petition was filed seven months after issuance).

B. No Other Forum Has or Is Currently Adjudicating Any Claim of the ’236 Patent

The lack of any other proceeding involving the ’236 Patent warrants denial of Patent Owner’s DDB. Where “parties [are] not involved in a parallel proceeding

involving the challenged claims... there is no concern of inconsistent outcomes or significant duplication of efforts.” (*Id.* at 2-3 (denying request for discretionary denial and referring the Petition to the Board).) Here, no proceeding—let alone one involving Petitioner—concerns the ’236 Patent and thus there is no risk of inconsistent results or duplicative effort. This factor supports denial.

C. Merits Are Very Strong

The Challenged Claims are directed to a group of GLP-1R agonists, encompassing, among others, Compounds 1, 19, 20, and 65. (EX1001, 204:1–220:58.) Petitioner has shown that each claimed compound would have been obvious over prior art not—at least adequately—considered by the Examiner.

In Ground 1, Petitioner demonstrates that Su identifies Compounds 175 and 44 as promising development leads and provides clear motivation for a POSA to modify them to arrive at claimed Compound 19. (Pet. 25-31, 46-57; EX1002, ¶¶60-70, 145-199; EXS1005, 1006, 1007, 1031.) Su identifies the need for further improvement of existing GLP-1R agonists and highlights the selection of seven stereoisomerically pure compounds out of hundreds for deuteration. In particular, the selective deuteration in Compounds 176 and 44 underscores the value of these compounds and their non-deuterated parent structures as leads. (Pet. 26-30; EX1002, ¶¶61-62, 149-151; EX1007, Examples 176, 44; EXS1005, 1031.) These leads also share the same core as the well-known Compound 67 and are reasonably expected

to be similarly active against GLP-1R. (*Id.*) A POSA would have been further motivated to apply Su's teachings, such as adding a cyclopropyl group and removing dimethyl groups as guided by the structures of the leads, to reach Compound 19. (Pet. 54; EX1002, ¶¶61–69, 153-154.) Petitioner further explains that Yoshino, Kawai, and Talele provide *additional* support for lead modifications. (Pet. 57-65.)

In Ground 2, Petitioner shows a POSA would have selected Compound 67 as a lead based on Yoshino, and be motivated to modify it based on Kawai and Talele, leading to Compounds 1, 19, and/or 20. (Pet. 83-105; EX1002, ¶¶200-267.)

In Ground 3, Petitioner explains that, seeking improved potency or pharmacokinetics, a POSA would have introduced a nitrogen atom at the relevant heteroaryl, consistent with modifications disclosed in Meng and Ren, thereby arriving at Compound 65. (Pet. 105-112; EX1002, ¶¶268-306.)

In Ground 4, Petitioner shows that the combined teachings of Su and Bethel render obvious the preparation of a ½ calcium salt of Compound 1. (Pet. 115-120; EX1002, ¶¶307-314; EX1032.)

In addition, the *Advanced Bionics* framework warrants denial of the DDB.

1. The Grounds Do Not Present Substantially Similar or Cumulative Prior Art

Patent Owner concedes that Su, Talele, Patel, and Pennington were not before the Examiner during prosecution. (DDB, 8-11, 22.) Since the Petition relies on these references in new combinations never considered by the Examiner, the first prong of

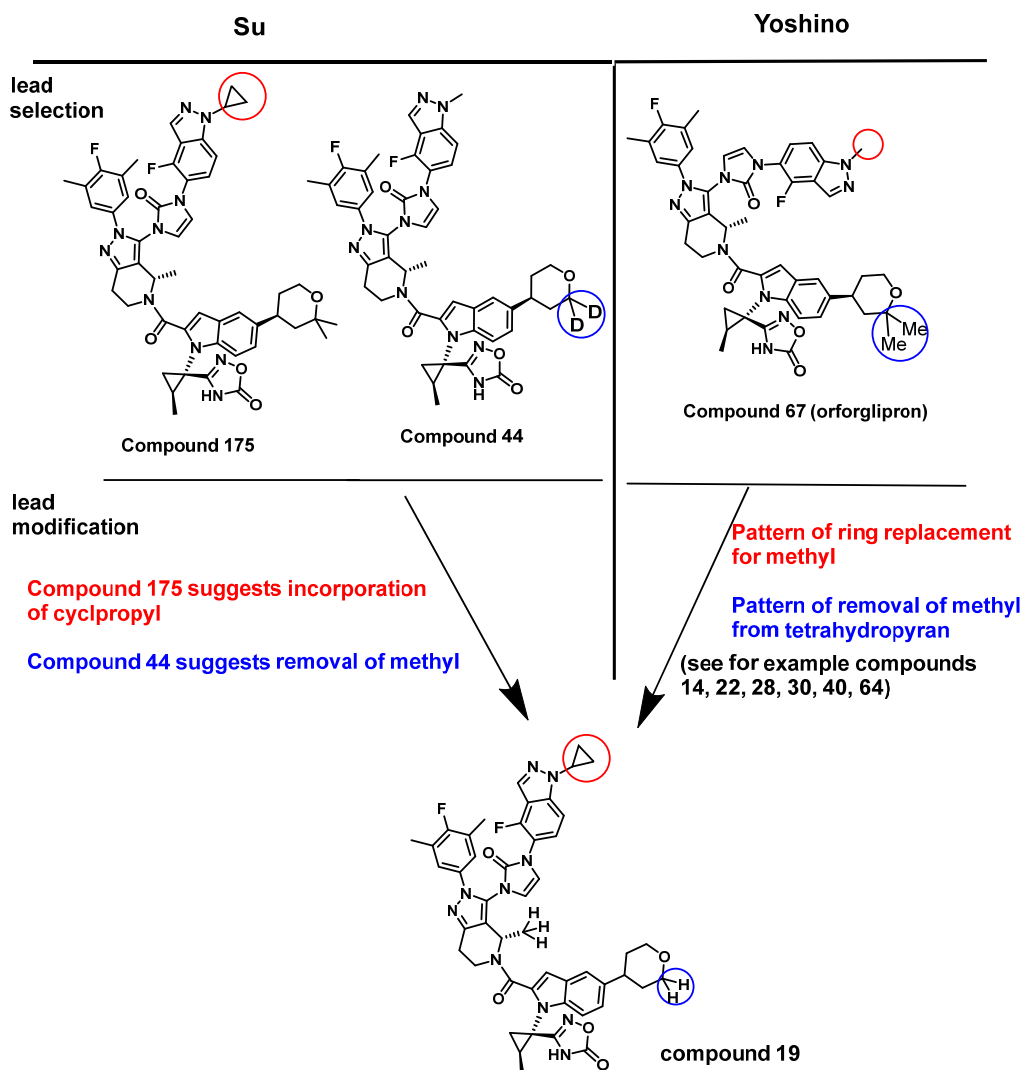
Advanced Bionics is not satisfied. See *Advanced Bionics*, IPR2019-01469, Paper 6 at 8-9; *Halliburton Energy Servs., Inc. v. U.S. Well Servs., LLC*, IPR2021-01036, Paper 12 at 20 (PTAB Jan. 19, 2022) (*Advanced Bionics* prong one not satisfied where obviousness grounds based on combinations involving a reference previously considered by the Examiner with other references that had not been considered); *ResMed Inc. v. New York Univ.*, IPR2022-00990, Paper 16 at 15-16 (PTAB Dec. 6, 2022) (first prong of the *Advanced Bionics* framework is not satisfied because “there are no rejections based on the combination of references asserted here.”).

Contrary to Patent Owner’s mischaracterization, there is no authority that impose on petitioners any obligation to compare a new reference against “all” of the hundreds of references dumped on the Examiner. (DDB, 7.) See, e.g., *Parse Biosciences, Inc. v. 10X Genomics, Inc.*, IPR2023-01033, Paper 8 (PTAB Dec. 19, 2023); *Alarm.com, Inc. v. Vivint, Inc.*, IPR2022-00728, Paper 6 (PTAB Nov. 1, 2022). Regardless, neither Su nor Talele are cumulative over the cited prior art.

a. Yoshino v. Su

Patent Owner’s comparison table highlights—not undermines—the substantial differences in how each reference approaches lead identification and modification. (DDB, 12-13.) Although both references ultimately involve cyclopropyl incorporation and methyl removal, their starting points, rationales, and guidance are fundamentally distinct. To determine whether a new chemical was

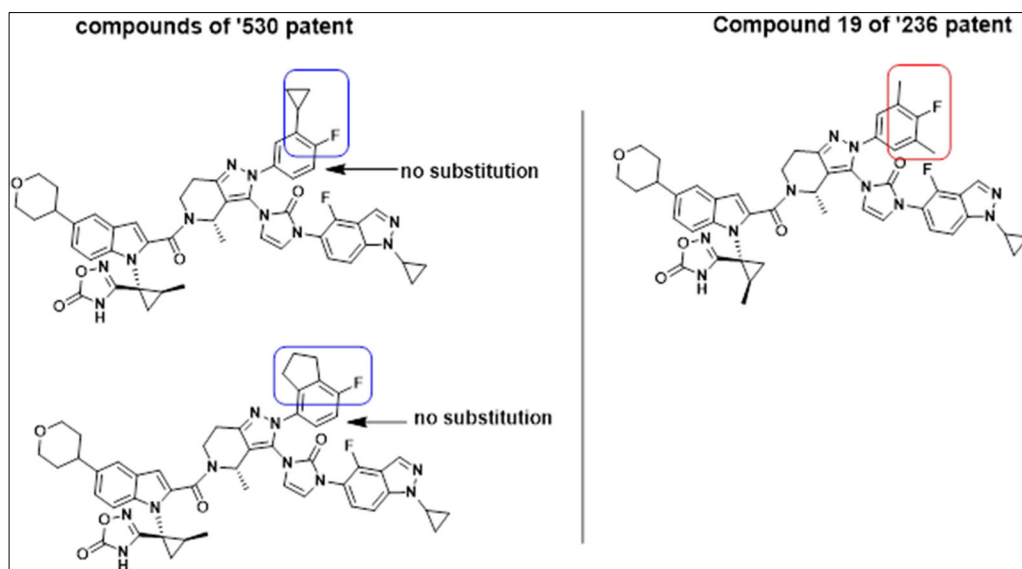
obvious, courts determine (1) whether a POSA would have selected the asserted prior art compound(s) as lead compound(s), or stating points for further development efforts, and (2) whether the prior art supplied a POSA with a reason or motivation to modify the lead compound. *See Otsuka Pharma. Co., Ltd. v. Sandoz, Inc.*, 678 F.3d 1280, 1291-93 (Fed. Cir. 2012). Su as shown in the figure below expressly identifies a small set of compounds, including Compounds 175 and 44, as leads. By contrast, Yoshino begins with Compound 67.



In addition, the lead compounds of Su provide limited and specific modification guidance on cyclopropyl incorporation, whereas Yoshino discloses a specific trend on indazole of replacing methyl with tetrahydropyran (THP), which led to comparable activities and even reversed the loss of activity (from compound 54 to compound 8). (Pet. 20-25; 54-61). Such a trend provides a strong motivation for using a cyclopropyl ring, which is even closer in size than THP to methyl. Likewise, Su's rationale for removing methyl groups stems from the unique features of lead Compound 44 with deuterium (D) replacing methyl, while Yoshino provides a clear trend of methyl removal across a series of compounds. (*Id.* 47-49, 54-56, 63-64; EX1002, ¶¶168-69.) Accordingly, Su and Yoshino reflect distinct approaches to both lead selection and modification, and Patent Owner's conflation of the two references improperly bypasses the two-step framework required for lead selection and lead modification.

Patent Owner speciously contends that the Office would have reached the same conclusion, *i.e.*, patentability over Su, because Su was considered during prosecution of the '530 Patent, which purportedly shares the "similar core structure" as claimed by the '236 Patent. (DDB, 19-20.) But the '530 Patent claims compounds with substitution patterns markedly different. Specifically, the claimed compounds in the '530 Patent place a ring (either pendant or fused to a phenyl) on only one side of a fluorine atom, leaving the other side unsubstituted. (EX2006, Claim 1.) In

contrast, Compound 19 of the '236 Patent bears two non-ring methyl substituents flanking the fluorine atom. (*Id.*; EX1001, Claim 1.)



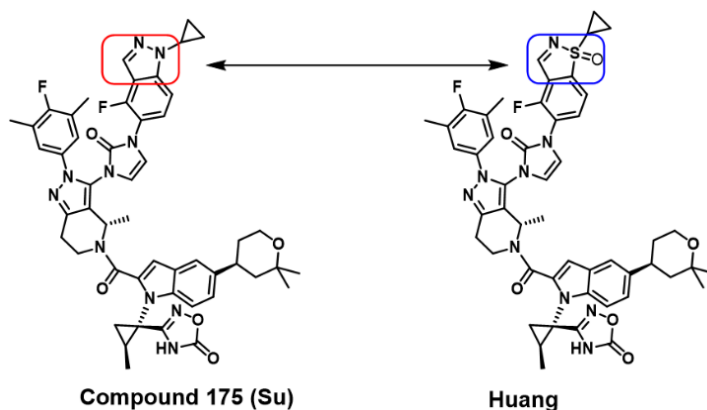
Thus, any reliance on the '530 Patent's prosecution is misplaced. Su's Compounds 175 and 44, which have two peripheral methyl groups flanking the fluorine, guide cyclopropyl incorporation and methyl removal, thereby leading to Compound 19. (Pet. 3-4; EX1002, ¶170.) But those same Su compounds fail to provide sufficient modification guidance toward the pendant or fused ring substitution patterns of the '530 Patent compounds. Accordingly, the fact that Su was considered during prosecution of the '530 Patent is irrelevant to the present analysis.

Finally, Patent Owner's "common core" theory collapses under its own logic. (DDB, 19-20.) If correct, any prior art compound sharing the same core of the compounds in the '530 Patent would be patentable over Su. That hypothetical result underscores the flaw in Patent Owner's reasoning, which misconstrues the principles

of lead selection and optimization under controlling case law.

b. Huang v. Su

Patent Owner identifies certain compounds in Huang, which contain a cyclopropyl group and a sulfonamide-containing ring, to incorrectly argue alleged cumulativeness with Su's Compound 175, which has an indazole core. (DDB, 13-14, EX1033, 128-129.) However, mere disclosure of a compound does not suggest it as a lead. *Daiichi Sankyo Co. v. Matrix Labs., Ltd.*, 619 F.3d 1346, 1352 (Fed. Cir. 2010).

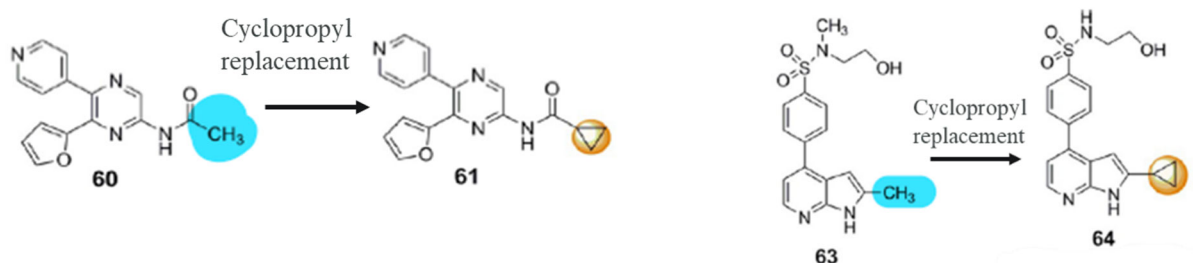


Here, Su expressly identifies Compounds 175 and 44 as leads and offers clear guidance for lead modification. (Pet. 46-66.) By contrast, Huang offers no teachings or guidance whatsoever on how one compound (out of 138 disclosed) should be selected as a lead, much less modified. (See generally EX1033.) Patent Owner's attempt to single out one compound in Huang based solely on the presence of cyclopropyl group ignores the law and principles of medicinal chemistry.

c. Huang/Kawai/Yoshino v. Talele

The assertion that Huang's cyclopropyl disclosures render Talele cumulative also lacks merit. (DDB, 9-10) Huang lists cyclopropyl among numerous substituents across 138 compounds, without teaching that cyclopropyl substitution was

significant or desirable. (*See generally*, EX1033.) Patent Owner offers no explanation for how such generalized disclosures establish a lead or motivate a POSA to modify the lead. Talele, by contrast, provides a focused and systematic analysis of cyclopropyl substitution as a well-established medicinal chemistry strategy, highlighting its favorable impact on drug-like properties. (Pet. 36; EX1002, ¶¶80-84; EX1009, 1.) It presents comparative examples *across diverse scaffolds*, demonstrating the consistent and intentional application of cyclopropyl substitution. (Pet. 36-37; EX1002, 82-84; EX1009, 13-14 (annotated).)



This targeted teaching is materially distinct from Huang's scattershot disclosure. Talele thus cannot be dismissed as cumulative. Meanwhile, Kawai and Yoshino generally teach replacing methyl with ring systems, whereas Talele specifically identifies the advantages of cyclopropyl replacement.

2. There Is Substantial Evidence the Office Materially Erred

The Examiner erred in allowing the '236 Patent by failing to recognize the materiality of several references, in part because Patent Owner inundated the record with hundreds of references without explanation. Critically, the Examiner neither identified a proper lead compound, nor considered prior art teachings on lead

modifications.

**a. *The Examiner’s Erred Patentability Determination
Occurred Prior to Patent Owner’s Dump of Hundreds
of References***

The Board has recognized that the timing and volume of IDS submissions may show the Examiner did not meaningfully consider the art. *Ecto World, LLC v. RAI Strategic Holdings, Inc.*, IPR2024-01280, Paper 13 at 6-7 (PTAB May 19, 2025) (precedential) (noting typical IDS included about 25 references, while patent owner submitted “over 40 times” that amount), Paper 16 at 13-14 (declining discretionary denial where record lacked evidence of substantive consideration). Likewise, in *Fellowes, Inc. v. Treefrog Devs., Inc.*, the Board found examiner error where the examiner was “inundated” with art but failed to apply the most relevant teachings. Paper 12 at 15-16 (PTAB Feb. 22, 2021).

That is precisely the case here. The Examiner conducted a search on the evening of October 28, 2024, generating a 528-page report listing hundreds of compounds, and signed the Statement of Reasons for Allowance the next day, ***days before*** any IDSs were submitted. (EX1003, 169, 176, 715.) Thereafter, between November 2 and 4, 2024 (Saturday to Monday)—and ***just two business days*** before the November 6, 2024 mailing date of the NoA—Patent Owner submitted ***hundreds of references*** totaling more than ***10,000 pages***, without identifying the relevant teachings. (*Id.* 176-703, 704-812.) This sequence indicates the Examiner did not

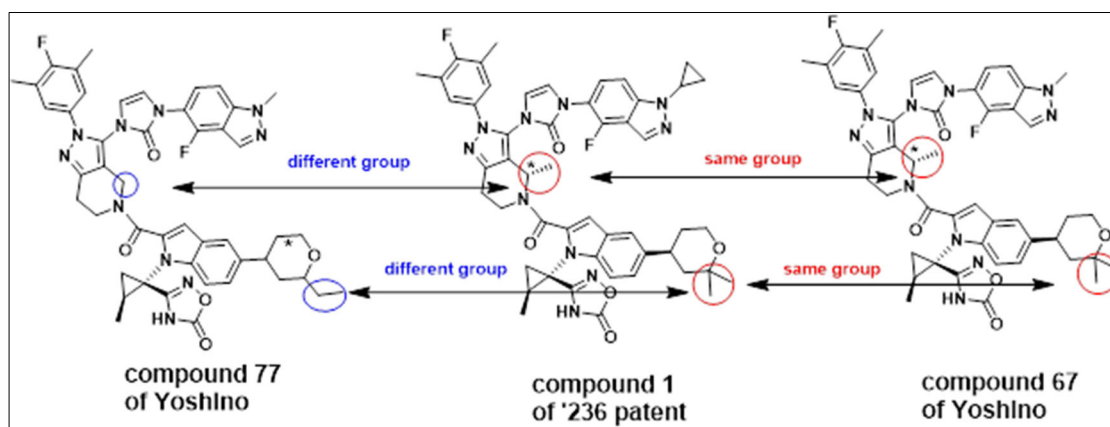
consider any later-submitted references in the IDSs before allowing the application. It is implausible that the Examiner could have meaningfully reviewed such a volume of material in that time. The allowance confirms as much: the Examiner cited only one compound from the search report and ignored the lead compounds and teachings on which Petitioner relies. (*Id.* 168.) The record therefore shows that the asserted prior art was not substantively reviewed or understood, underscoring clear error.

b. The Examiner Failed to Select a Suitable Compound As a Lead During Prosecution

The NoA reflects the Examiner's error in failing to identify an appropriate lead compound from the art. As explained herein, Su directed a POSA to Compounds 175 and 44 as leads. There is no dispute that the Examiner never considered Su, let alone these compounds. Likewise, Compound 67 (orforglipron) is repeatedly emphasized in Yoshino 33 times and exclusively discussed in Kawai. (*See generally* EXS1004, 1008.) It is also the only compound tested in animal models in both references. (EX1004; EX1008, Test Examples 3-4, FIGS. 5-6, 8-12.) However, and without any explanation, the NoA relies exclusively on Compound 77, which Yoshino mentions only twice. (Pet. 11; EX1008, Example 77, Table 3.)

The structural differences between Compounds 67 and 77 are substantial. Compound 67, which closely resembles Compound 1 of the '236 Patent, contains a chiral center with a methyl substituent in the core heterocyclic ring, whereas Compound 77 lacks both. (EX1008, 99, 121.) Compound 67 also contains a

di-methyl-substituted non-chiral carbon in the tetrahydropyran ring, whereas Compound 77 contains a mono-substituted chiral carbon in the pyran ring. (*Id.*; EX1001, Claim 1(annotated).)



Given the central role of Compound 67 in Yoshino and Kawai, a reasonable examiner would have cited it. The Examiner's unexplained reliance on Compound 77 in his/her NoA, without discussion of Compound 67, shows Yoshino was not meaningfully evaluated, alone or in combination with other art.

Patent Owner's assertion—Compound 67 (orforglipron) “must have been considered” simply because it was repeatedly mentioned in the prosecution history and used as a comparator in the '236 Patent—is unfounded. (DDB, 18.) Mere reference in search reports or prior art do not establish substantive evaluation by the Examiner. The utter lack of discussion of Compound 67 during prosecution, despite its repeated emphasis in Yushino and exclusive discussion in Kawai, highlights the Examiner's failure to recognize its significance, and constitutes material error precluding Patent Owner's request for discretionary denial. *See Klein Tools, Inc. v.*

Milwaukee Elec. Tool Corp., IPR2024-01400, Paper 17 at 25-26 (PTAB April 8, 2025) (finding material error where despite patent owner’s argument that the examiner clearly understood the art, “[g]iven the prosecution history’s silence on Burchia and Metabowerke, however, we do not view the alleged understanding as in any way ‘clear[.]’”) (emphasis added); *Amazon.com Inc. v. Nokia Tech.*, IPR2024-01140, Paper 9 at 16 (PTAB February 12, 2025) (finding material error where the prosecution was “*silent*” as to the key prior art and “*there was no discussion or analysis of [this art] apart from its inclusion on the IDS.*”).

Patent Owner further misapplies *Eli Lilly & Co. v. Zenith Goldline Pharms., Inc.* in arguing that Su’s Compound 175 cannot qualify as a lead compound absent activity data. *Eli Lilly*, 471 F.3d 1369 (Fed. Cir. 2006); DDB, 18-19. *Eli Lilly* imposed no such categorical rule. The court there rejected a non-halogenated compound as a lead because the prior art expressly preferred halogenated compounds in direct comparison with the non-halogenated counterparts, identified a specific fluorine-containing compound as “particularly active,” and taught that halogen substitution enhanced activity. *Id.* 1379. The court’s reference to biological data was incidental; it did not hold that the absence of activity data alone precludes a compound from serving as a lead. *Id.* Patent Owner cites no authority barring consideration of factors such as structural novelty, synthetic feasibility, pharmacokinetics, or optimization potential, even without direct biological activity

data. Petitioner's expert, Dr. Pirrung, explains that Su expressly identified compounds, including Compound 175, for deuteration—a recognized medicinal chemistry strategy to enhance pharmacological traits of drug candidates. (EX1002, ¶62.) This deliberate focus confirms that Compound 175 was regarded as a promising lead, regardless of whether direct activity data was reported.

c. The Examiner Failed to Properly Combine Yoshino and Kawai for Lead Selection and Lead Optimization

The Examiner never expressly considered Kawai, which discusses solely Compound 67. The Examiner disregarded Kawai for both lead selection and lead optimization in view of Yoshino.

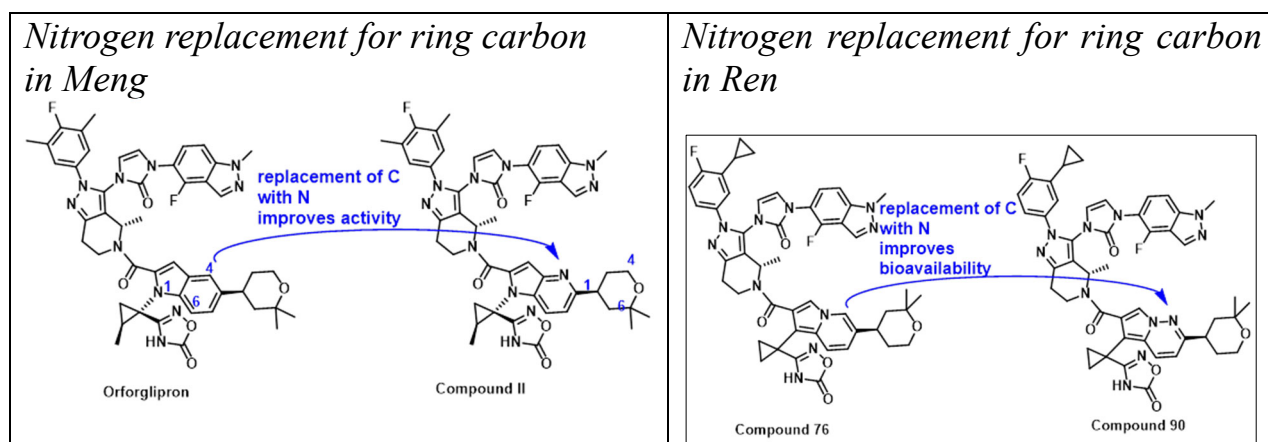
Kawai provides a detailed 3D protein-ligand interaction model illustrating the binding pocket around Compound 67. (Pet. 33; EX1002, ¶¶52-59; EX1004, FIG. 11.) The model shows that the region adjacent to the methyl group on the indazole moiety can readily accommodate a bulkier substituent. (Pet. 35; EX1002, ¶58.) Yoshino complements this teaching by demonstrating a consistent substitution pattern at this very position, replacing the methyl group with a ring structure. (Pet. 92; EX1002, ¶¶210-13.) Together, Kawai and Yoshino would have directed a POSA to consider a cyclopropyl substituent—being the cycloalkyl ring most closely analogous in size to a methyl group—as a logical optimizing modification. (Pet. 92; EX1002, ¶213.)

As further discussed *infra*, Talele corroborates this rationale by explaining the well-recognized advantages of substituting a small alkyl group with a cyclopropyl

ring across diverse chemical scaffolds, thus reinforcing the guidance for lead optimization. (Pet. 92-94; EX1002, ¶¶214.)

3. Ground 3 Satisfies the Advanced Bionics Framework

Meng and Ren, each analyzing analogs of orforglipron (Compound 67), expressly describe nitrogen replacement at the identical ring carbon as shown below. Together, Meng and Ren confirm that this nitrogen replacement strategy applies broadly, including to analogs such as Compound 19. (EX1002, ¶¶274-284.)



(Pet. 107, 110; EX1002, ¶¶275, 281.)

Patent Owner incorrectly characterizes Meng, Ren, Patel, and Pennington as “cumulative.” As illustrated above, these references provide distinct and complementary teachings regarding nitrogen incorporation for analogs of orforglipron. Meng and Ren highlight the feasibility and benefits of replacing a ring carbon with nitrogen in heteroaromatic systems, while Patel and Pennington supply the broader chemical rationale for such replacements and their predictable pharmacological effects. (Pet. 108-112; EX1002, ¶¶278-280.) Together, they offer a

unified and compelling motivation to modify Compound 19 in precisely the manner that yields Compound 65. (Pet. 108; EX1002, ¶277.) This collective teaching reflects synergy, not cumulative disclosure, and thus the Examiner erred.

4. Ground 4 Satisfies the Advanced Bionics Framework

As discussed, Su is not cumulative of Yoshino and Huang. The Petition demonstrates how Su (not before the Examiner), when combined with Bethel, renders the hemicalcium salts of claims 4 and 9 obvious. (Pet. 115-116; EX1002, ¶¶307-314.) The fact that the Petition explicitly addresses the role of Su in teaching the base compounds, and Bethel in teaching hemicalcium salt formation, is sufficient to show that the Examiner erred. (Pet. 115-116.) Patent Owner's reliance on *Pfizer Inc. v. Apotex Inc.*, backfires, as the case held salt formation can be unpredictable but that "obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success." *Pfizer Inc. v. Apotex Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007). Here, because Bethel teaches only the hemicalcium salt of orforglipron in clinical trial, it represents the obvious choice for forming a pharmaceutically acceptable salt, as claimed, with a reasonable expectation of success. (*See generally* EX1032.) The Examiner's failure to appreciate this resulted in a patentability determination error.

5. Petitioner's Application Is Irrelevant to Consideration

Patent Owner's reliance on an application filed by Petitioner is misplaced. The

mere existence of Petitioner's earlier application does not demonstrate that the claims at issue are patentable. Critically, Petitioner did not conduct a comprehensive prior art search when CSPC's applications were filed and therefore lacked a complete understanding of the relevant art. Any preliminary view of patentability at that time was necessarily provisional and subject to change upon a full prior art review. Patentability assessments evolve as new prior art is identified. Moreover, because CSPC's international application has not yet entered the U.S. national stage, Petitioner retains ample opportunity to amend the claimed subject matter.

D. Patent Owner Concedes That Most of the Considerations Outlined In the Director's Memo Weigh Against an Exercise of Discretionary Denial

Patent Owner does not address any of the additional factors outlined in the Director's Memo and thus concedes they do not support denial. (*See supra* Section II (outlining considerations) *with generally* Paper 9 (failing to address considerations, *e.g.*, improper reliance on expert testimony, settled expectations, compelling economic/public health interests, etc.).)

IV. CONCLUSION

Based on the foregoing, the Board should decline to exercise discretionary denial under § 325(d).

Dated: October 8, 2025

By: /Jin Zhu/

Jin Zhu, Ph.D.

Reg. No. 62,869

Counsel for Petitioner

CERTIFICATE OF COMPLIANCE

Pursuant to the Interim Director's Discretionary Process, Section III.C.iii, the undersigned certifies that the foregoing Petitioner's Response to Patent Owner's Request for Discretionary Denial of Institution is 20-pages or less.

Dated: October 8, 2025

By: /Joe Chen/
Joe G. Chen, Ph.D.
Reg. No. 70,066
Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.6(e), I hereby certify that on October 8, 2025, I caused a true and correct copy of the foregoing Petitioner's Response to Patent Owner's Request for Denial of Institution to be served by electronic mail, as authorized by Patent Owner, at the following email addresses:

Lead Counsel

W. Chad Shear, Reg. No. 47,938
cshear@cooley.com

Backup Counsel

Geoffrey D. Biegler, (*pro hac vice* forthcoming)
gbiegler@cooley.com

Dated: October 8, 2025

By: /Joe Chen/
Joe G. Chen, Ph.D.
Reg. No. 70,066
Counsel for Petitioner