

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

BONERGE LIFESCIENCE (HUNAN) CO., LTD.,
Petitioner

v.

NANJING NUTRABUILDING BIO-TECH CO., LTD.,
Patent Owner

U.S. Patent No. 10,278,961
Filing Date: April 19, 2017
Issue Date: May 7, 2019
Title: Administration of berberine metabolites

Inter Partes Review No.: IPR2025-01593

**PETITIONER'S OPPOSITION TO PATENT
OWNER'S DISCRETIONARY DENIAL BRIEF**

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LIST OF PETITIONER'S EXHIBITS

No.	Description
1001	U.S. Patent No. 10,278,961
1002	Excerpts of Prosecution File History of U.S. Patent No. 10,278,961
1003	Expert Declaration of Dr. Ronald J. Shebuski, Sr.
1004	Nigel Turner et al., Berberine and Its More Biologically Available Derivative Dihydroberberine, Inhibit Mitochondrial Respiratory Complex I, Diabetes, Vol. 57, May 2008, 1414-1418 (“Turner”)
1005	Shannon Reagan-Shaw et al., Dose translation from animal to human studies revisited, The FASEB Journal, Vol. 22, March 2007, pp. 659-661 (“Shaw”)
1006	Yifei Zhang et al., Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine, J. Clin Endocrinol Metab, July 2008, 93(7):2559-2565. (“Zhang”)
1007	Ru Feng et al., Transforming berberine into its intestine-absorbable form by the gut microbiota, Nature Scientific Reports, 5:12155, DOI: 10:1038/srep12155, published July 15, 2015 (“Feng”)
1008	Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers, USFDA, Center for Drug Evaluation and Research (CDER), July 2005 (“FDA Guidance”)
1009	Chunqiu Chen et al., A randomized clinical trial of berberine hydrochloride in patients with diarrhea-predominant irritable bowel syndrome, Phytotherapy Research, 29:1822-1827 (2015) (“Chen”)
1010	Li Liu et al., Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states, evidences from in vivo and in vitro study, Naunyn-Schmied Arch Pharmacol, March 2013, 381:371–381. (“Liu”)

No.	Description
1011	Aillen JF King, The use of animal models in diabetes research, British Journal of Pharmacology, (2012) 166 877-894. (“King”)
1012	U.S. Application 12/443,401, published on May 6, 2010 as US 2010/0113494. (“Hu”)
1013	Declaration of Hua Chen
1014	Patent Assignment Record of U.S. Patent No. 10,278,961
1015	<i>Longitude Licensing Ltd., v. Amazon.com, Inc. & Western Digital Tech. Inc.</i> , No. 23cv0039 (C. D. Cal. Feb. 26, 2024)
1016	<i>Polaris PowerLED Technologies, LLC v. VIZIO, Inc., et al</i> , No. 23cv3478 (C. D. Cal. April 8, 2024)

I. INTRODUCTION

The main claim challenged in the IPR2025-01593 petition recites a method of “managing glucose tolerance in an individual” by administering to an individual “approximately 25 mg to approximately 800 mg of dihydroberberine.” Dihydroberberine is a derivative of berberine, which is a decade-old nonprescription oral medicine used in China to treat diarrheas with few side effects. Prior to the filing of the ’961 patent at issue, it had been well established, via numerous clinical studies, that berberine is effective for diabetes treatment. Also before the critical date, it had been widely reported that dihydroberberine is more bioavailable than berberine, and that dihydroberberine is effective for diabetes treatment via animal studies. The Petitioner presents a few key research papers in the IPR2025-01593 petition; the Patent Owner (PO) now seeks a discretionary denial.

Discretionary denial is not warranted because all of the *Fintiv* factors point in one direction – institution. The anticipated final written order date will issue before the tentatively scheduled trial date in the district court litigation. Petitioner’s broad stipulation guarantees no overlap between the instant IPR proceedings and the district court litigation. The district court litigation is still in its early stages; the Court is not expected to issue any order related to the ’961 patent before the projected institution decision date. Petitioner will renew its motion to stay once the IPR is instituted, as the Court explicitly permits, with a high chance of staying the district

court action. PO has no settled expectations – (1) it did not invent but instead purchased the '961 Patent from a patent holding company in 2021, which makes the length of any settled expectation less than 4 years, far less than the 6 year benchmark; (2) it has not licensed of the '961 patent and has not asserted it until the instant district court litigation; (3) the patent office committed material errors during the prosecution of the '961 patent where it misinterpreted and misapplied the teachings of the main prior art reference on the record. Lastly, the Petition presents strong meritorious invalidity grounds especially in view of the broad scope of the challenged claims.

II. DISCRETIONARY DENIAL IS NOT WARRANTED

A. *Fintiv* Factor 1 (Stay) Weighs against Discretionary Denial

Fintiv factor 1 “weigh[s] against exercising authority to deny institution” in a case where, as here, “the district court has denied a motion for stay without prejudice and indicated to the parties that it will consider a renewed motion ... to stay if a PTAB trial is instituted.” *Apple Inc. v. Fintiv, Inc.*, IPR2020-00019, Paper 11 at 6-7 (PTAB Mar. 20, 2020) (“*Fintiv*”). A Court’s willingness to stay parallel litigation post-institution can be manifested if “such guidance from the district court” is “made of record.” *Id.* at 7. Here, the Court ordered the parties to provide a status report “within seven days of a decision by PTAB on whether to initiate IPR,” and “[a]t that time, if IPR is initiated, [Petitioner] is free to again move for a stay.” Ex.

2015 at 4. If the Board institutes IPR against the '961 patent, and Petitioner renews its motion to stay (which Petitioner will), there is a strong likelihood that the Court will grant the renewed motion to stay. *See C.R. Laurence Co., Inc. v. Frameless Hardware Co. Ltd. Liab. Co.*, No. 2:21-cv-01334-JWH-RAO, 2022 U.S. Dist. LEXIS 247028 (C.D. Cal. Dec. 9, 2022) (granting a renewed motion to stay after PTAB instituted IPRs for two asserted patents); *Longitude Licensing Ltd., v. Amazon.com, Inc. & Western Digital Tech. Inc.*, No. 23cv0039, slip opinion (C. D. Cal. Feb. 26, 2024) (order granting renewed motion to stay pending IPR) (Ex. 1015).

Furthermore, because the investment by the parties and the Court is limited, the Court's willingness to consider a renewed motion to stay should be accorded with heavy weight. *Cf. Fintiv* at n. 11-12. As detailed in *Fintiv* factor 3 analysis below (§II.C), there is still significant amount of work left to be done in the parallel litigation after the projected April 7, 2026 institution deadline, including claim construction work by the Court (the claim construction hearing is scheduled for April 21, 2026, or as soon thereafter as possible), most of fact discovery, any expert discovery, and dispositive motions. Courts, including courts from the central district of California here, have stayed proceedings post-institution where the litigation has not proceeded far along. *See Cao Lighting, Inc. v. Signify N. Am. Corp.*, No. CV 21-08972-AB (SP), 2022 U.S. Dist. LEXIS 244450, at *7 (C.D. Cal. Dec. 21, 2022) ("There is a near uniform line of authority [reflecting the principle that] after the

PTAB has instituted review proceedings, the parallel district court litigation ordinarily should be stayed.”) (internal citation omitted). In fact, courts have granted renewed motions to stay in cases where the parties and the Court have already invested significant amounts of work than what is invested in the instant case. *See Polaris PowerLED Technologies, LLC v. VIZIO, Inc., et al*, No. 23cv3478, slip opinion (C. D. Cal. April 8, 2024) (scheduling order granting renewed motion to stay despite Court having issued a tentative ruling on claim construction) (Ex. 1016); *C.R. Laurence Co., Inc.*, 2022 U.S. Dist. LEXIS 247028 (granting a renewed motion to stay despite the Court’s prior ruling on a preliminary injunction motion); *Bell Northern Research, LLC v. Coolpad Technologies, Inc.*, 18-CV-1783-CAB-BLM, 2020 WL 13157794, at *2 (S.D. Cal. Feb. 18, 2020) (granting renewed motion to stay despite parties having concluded fact and expert discovery and filed dispositive motions).

B. *Fintiv* Factor 2 (Trial Date) Supports Institution

The PO does not dispute that the projected Final Written Decision deadline is April 7, 2027, weeks before the currently scheduled April 20, 2027 district court trial date. *See* DD Br. at 9. Moreover, delay is likely in the district court action given the congestion of the district courts in the central district of California. The trial date is likely to be even further delayed given the likelihood the district court will grant Petitioner’s renewed motion to stay if the Board grants institution. *See supra* §II.A.

Furthermore, the Court and the parties have not invested significant resources in parallel proceeding, for reasons stated in §II.A above and §II.C below. Thus, *Fintiv* factor 2 supports institution.

PO's reliance on *Advanced Micro Devices, Inc. v. Concurrent Ventures, LLC* (DD Br. at 9) is misplaced because the case schedule there is materially different. There, the scheduled trial date is weeks *before* the projected final written decision due date, which led the Board to conclude that "it is unlikely that a final written decision ... will issue before the district court trial occurs." IPR2025-00223, Paper 9, at *2 (PTAB June 12, 2025). Also in the *Advanced Micro Devices* situation, the "*Markman* hearing is scheduled to occur before the due date for an institution decision." *Id.* Here, the trial date is scheduled weeks *after* the statutory deadline for the final written decision, and the *Markman* hearing is scheduled weeks *after* the statutory deadline for the institution decision (and the District Court judge has ordered the parties to provide a status report on PTAB's institution decision before the *Markman* hearing date). In contrast to the *Advanced Micro Devices* situation, the current district litigation schedule would result in significant savings of judicial and party resources if the Director denies PO's discretionary denial request. *Cf. Fintiv*, IPR2020-00019, Pap. 11 at 9 ("If the court's trial date is earlier than the projected statutory deadline, the Board generally has weighed this fact in favor of exercising authority to deny institution under *NHK*.").

C. *Fintiv* Factor 3 (Parallel Proceeding) Weighs against Discretionary Denial

The district court has not made a single substantive ruling regarding the '961 patent to date. The district court will not issue any substantive ruling regarding the '961 patent at the time of the institution decision. This factor weighs against discretionary denial. *Fintiv*, IPR2020-00019, Pap. 11 at 10 (“If, at the time of the institution decision, the district court has not issued orders related to the patent at issue in the petition, this fact weighs against exercising discretion to deny institution under *NHK*.”).

Contrary to PO’s assertions, the parties have not invested “heavily” in the district court litigation. The following procedure stance of the district court litigation is not disputed. No party or expert deposition has been noticed, and no case-dispositive motions have been filed (dispositive motion hearing deadline not until February 22, 2027). Ex. 1013, ¶¶ 3, 4. Plaintiff has served only one initial set of written discoveries to Defendant Bonerge Lifescience (Hunan) Co., Ltd. (which was answered). Ex. 1013, ¶ 5. A minimum number of documents - aggregating slightly over three thousand pages and covering only a few hundred documents - have been produced by both parties. *Id*, ¶ 6. Claim construction is also in its early phases—the parties’ claim construction briefs are not due until March 12, 2026. *Id*, ¶ 7. The *Markman* hearing is currently scheduled for April 21, 2026 and possibly later —weeks after the Board’s institution deadline. *Id*, ¶ 8. In fact, the Board has

granted institution in cases that are more advanced than here. *See Samsung Display Co. v. Pictiva Displays Int’l Ltd.*, IPR2024-01222, Paper 12 at 7 (PTAB Mar. 6, 2025) (factor 3 weighs against denial, even after *Markman* hearing was held because “much remains to be done, including expert discovery”); *SAP Am., Inc. v. Cyandia, Inc.*, IPR2024-01432, Paper 14 at 8-9 (PTAB Apr. 7, 2025) (factor 3 favors institution even after *Markman* briefing was complete).

D. *Fintiv* Factor 4 (Issue Overlap) Weighs Strongly in Favor of Institution

Petitioner’s broad *Sotera*-plus stipulation guarantees no overlap between the instant IPR proceedings and the district court litigation, and thus strongly favors institution. Petitioner’s broad *Sotera*-plus stipulation eliminates any overlap with the district court case, alleviating any concerns about inefficiency or inconsistency. Petitioner’s stipulation includes two parts: (1) a standard “*Sotera* stipulation,” and (2) an additional stipulation precluding any 102 and 103 invalidity grounds, including system arts. Specifically, the stipulation recites:

Bonerge hereby stipulates that, should the PTAB institute review of the Petition, it would not pursue in the district court litigation (Case No. 25-cv-00271, filed in C. D. Cal.) any grounds that are raised or reasonably could have been raised in the IPR. Bonerge hereby further stipulates that, should IPR2025-01593 be instituted, it would not pursue in the district court litigation any invalidity grounds under 35 U.S.C. §§ 102 and 103 against the ’961 Patent—including those grounds with system prior art.

Ex. 3001. Additional Section 112 grounds the Petitioner raises in the district court

case would not cause duplicative efforts or inconsistent rulings (DD Br. 12), as those are beyond the Board's statutory jurisdiction. 35 U.S.C. §311(b).

PO contends that Petitioner's "*Sotera* statement to the Board is of minimal import ... where other grounds of invalidity are presented in the litigation." The argument does not withstand scrutiny, and the case law PO cited are inapposite. DD Br. at 13. As shown above, Petitioner's stipulation is much broader than a standard "*Sotera* stipulation." In fact, a stipulation similar to Petitioner's has been found to weigh against discretionary denial. *See Shenzhen Tuozhu Technology Co., Ltd. v. Stratasys, Inc.*, IPR2025-00438, Paper 10 at 3 (Director July 17, 2025) (finding "broad stipulation" precluding combination with system art weighed against discretionary denial).

Moreover, challenging additional claims (the petition includes a claim that is not asserted in the district court case) beyond those involved in the district court weighs in favor of institution as the district court will not reach these issues. *Fintiv*, IPR2020-00019, Pap. 11 at 10, 13 (challenging non-overlapping claims weighs "against exercising discretion to deny institution" if the challenged claims are not "similar[]" to "those at issue in the district court.").

E. *Fintiv* Factor 5 (Same Party) Favors Institution

This factor weighs in favor of referral and institution because although Petitioner and PO are the same parties as in the district court, the Board will address

the patent first here. *See Google LLC v. Parus Holdings, Inc.*, IPR2020-00846, Paper No. 9 at 21 (Oct. 21, 2020) (“Petitioner is the defendant in the parallel proceeding. This fact could weigh either in favor of, or against, exercising discretion to deny institution, depending on which tribunal was likely to address the challenged patent first.”); *see also Huawei Tech. Co. v. WSOU Inv., LLC*, IPR2021- 00225, Paper 11, at 14 (June 14, 2021) (“this factor ‘favors denial if trial precedes the Board’s Final Written Decision and favors institution if the opposite is true’”). At a minimum, this factor is neutral. *See HP Inc. v. Slingshot Printing LLC*, IPR2020-01084, Paper 13 at 9 (PTAB Jan. 14, 2021).

F. *Fintiv* Factor 6 (Other Considerations) Weighs Against Discretionary Denial

1. PO’s Claimed Expectations Are Far From Settled

First and foremost, PO can have no settled expectations because the Patent Office committed material errors during the prosecution of the ’961 patent. *See Anthony Inc. v. Controltec LLC*, IPR2025-00559, Paper 9 at 2 (Director July 16, 2025) (“*Anthony Inc.*”) (finding that “[a]lthough the challenged patents have been in force for approximately eighteen and seventeen years, Petitioner appears to show a material error by the Office, and it is an appropriate use of Office resources to review the potential error”). These material errors are explained in detail below (§II.F.4).

Second, PO’s “settled expectations” argument is based solely on the issuance date of the patent. *See DD Br.* at 13-14 (“[s]ettled expectations exist as to the ‘261

[sic] Patent, which issued on May 7, 2019, over 6½ years ago.”). Not so! On November 5, 2021, PO purchased the ’961 patent from the prior assignee (Keto Patent Group, Inc.), who owned the patent since May 7, 2019. *See* Ex. 1014. As its name suggests, the prior assignee (Keto Patent Group, Inc.) is a patent holding company. There is no evidence that it has ever commercialized the ’961 patent. Thus, if PO had any expectation as to the ’961 patent, such expectation did not start until the date of its acquisition, which shortens any purported “settled expectations” to under 4 years (*i.e.*, November 5, 2021 to October 7, 2025), far shy of the six-year benchmark. Indeed, prior to November 5, 2021, PO had no rights to commercialize, assert, mark, license, or otherwise apply the ’961 patent. *See Intel Corp. v. Proxense, LLC*, IPR2025-00327, Paper 12 at 2-3 (Director June 26, 2025) (“*Intel*”). The cases cited by PO all involve patents that have been actively practiced by their owners for six years or more. These cases are therefore inapplicable. *See* DD Br. at 14-15.

Third, recent decisions have indicated that the “settled expectations” timeframe should be measured from the date the patent was first practiced and commercialized or was otherwise enforced in the relevant technical field. *See Intel*, Paper 12 at 2–3 (“a patent may have been in force for years but may not have been commercialized, asserted, marketed, licensed, or otherwise applied in a petitioner’s particular technology space” are “non-exclusive examples...that weigh against a patent owner’s claim of settled expectations.”). The ’961 patent has not been

licensed or asserted against anyone until late 2024 (the current dispute against the Petitioner). Thus, PO cannot credibly claim that any expectation has been long settled because the strength and licensing potential for the '961 patent has not been tested in the marketplace. *See Shenzhen*, IPR2025-00438, Pap. 10 at 3 (Director declined to exercise discretionary denial for all challenged patents in a set of IPRs even though one of them had been “in force for approximately 10 years,” because that older patent had not been “asserted, ... licensed”).

Thus, the “settled expectations” factor does not favor a discretionary denial.

2. Expert Testimony Supports, Not Undermines, Institution

PO argues that Petitioner excessively relies on expert testimony and lists the number of cross references between the petition and the expert declaration. *See DD Br.* at 15-17. But the number of cites of an expert declaration alone does not support discretionary denial. *See, e.g., iRhythm Techs., Inc. v. Welch Allyn, Inc.*, IPR2025-00363, -374, -376, -377, -378, Paper No. 10, at 2–3 (PTAB June 6, 2025) (rejecting Patent Owner’s accusation that “Petitioner is over-reliant on expert testimony” and noting that “Petitioner is [not] using its expert to fill gaps in the prior art. Instead, Petitioner appears to rely on its expert to explain the background knowledge of a person of ordinary skill in the art, and the expert provides citations to evidence in support of his statements in the required manner.”); *Razdog Holdings LLC v. Twitch Interactive, Inc.*, IPR2025-00307, Paper No. 18, at 3 (PTAB May 16, 2025) (denying

request for discretionary denial despite the petition “cit[ing] its expert’s 269-page declaration at least 260 times”). That an expert would be frequently cited throughout the petition is not surprising as the petition must be supported with evidence and not mere attorney argument.

PO also ignores the dependent nature between the petition and expert declaration, which are hand-to-hand. Even though some portions of the expert declarations are referenced in the petition, using certain portions of expert opinion verbatim in the Petition (at least to the extent the 14,000-word limit allows) is a fail-safe way to ensure those expert opinions are fully considered by the Board given that the Board does not consider arguments incorporated by reference. *See, e.g., Group III Int’l, Inc. v. Targus Int’l LLC*, IPR2021-00371, Paper 21 at 28 (“To the extent Petitioner attempts to incorporate arguments from the exhibits into the Petition, we do not consider such arguments.” (citing 37 C.F.R. § 42.6(a)(3) (“Arguments must not be incorporated by reference from one document into another document.”))). A Petition is not an exercise in creative writing or thesaurus usage such that the evidentiary weight afforded to expert opinion is contingent upon the number of clerical rewrites of that expert’s chosen words and phrases.

Contrary to PO’s allegation that the “expert is filling gaps in the prior art,” (DD Br. at 16), the cited portions of the expert declaration contain a clear summary of the motivation to combine, referencing the prior art and explaining why a person

of ordinary skill in the art (POSITA) would have combined their teachings with reasonable expectation of success. Thus, Petitioner’s expert testimony serves as an aid to the Board, especially on issues like motivation to combine and reasonable expectation of success. PO fails to identify any specific “gaps” allegedly filled by the expert, and it is not the Director’s role to search the record for such supposed gaps when the PO has not identified any.

PO complains that Petitioner’s alleged extensive reliance would likely create factual disputes that is better addressed by a district court. *See* DD Br. at 17. On the contrary, given its expertise in the technical area, the Board is better or at least as well-equipped to address the disputes between the experts and has done so many times since the inception of the AIA. This further supports institution and weighs against discretionary denial.

3. The Strength of the Petition

The challenged independent claim recites a method of “managing glucose tolerance in an individual” by administering to the individual dihydroberberine at “approximately 25 mg to approximately 800 mg.” As stated in the Petition, dihydroberberine is a derivative of berberine, a decade-old nonprescription oral medicine used in China to treat diarrheas with few side effects. *See* Petition at 3. The Petitioner presents alternative grounds of invalidity. One ground is based on a combination of references reporting pre-clinical studies of dihydroberberine on

diabetic rodent models and FDA recommended animal-to-human dosage conversion methods. *See id.* at 27-32. An alternative ground is based on a combination of clinical study reports that berberine is effective for treating diabetes and research papers that conclude dihydroberberine is more bioavailable than berberine based on both in vivo (animal) and in vitro (human) studies. *See id.* at 48-55.

PO criticizes the merits of the Petitioner's invalidity arguments by cherry picking few academic review articles generalizing the unpredictability of extrapolating animal test results (*e.g.*, rodents) to humans. *See* DD Br. at 18-20. PO overstates the findings of these articles. They merely caution against overreliance on animal experiments which are oftentimes poorly designed; these articles do not advocate abandoning animal studies in drug development. For example, the main criticism in Pound is directed at “[p]oorly designed studies and lack of methodological rigour in preclinical research.” Ex. 2018, p. 002. Pound nevertheless acknowledges that “[m]uch clinical research follows on from animal research.” *Id.* What the authors advocate for is “urgent attention ... be paid to the quality of animal research.” *Id.* The Small paper that is co-authored by Turner (first author for one of the main prior art references in the Petition) advocates “more attention ... to be given to the total macronutrient content and composition when interpreting dietary effects on insulin action” while acknowledging that “[r]odent dietary models remain

an important tool for exploring potential mechanisms of insulin resistance.” Ex. 2019, p. 001 (abstract). In fact, the Small paper states that “Rat and mice dietary models investigating insulin action are therefore still required, as they have more relevance to human diet induced metabolic syndrome than monogenic models of insulin resistance and provide important tools for the evaluation of novel therapeutic agents for insulin resistance and type 2 diabetes.” *Id.* at p. 009. Finally, the Lai paper acknowledges that a high fat diet rodent model is widely popular and trending. *See* Ex. 2020, p. 001 (“A simple PubMed database search (using the keywords ‘high fat diet’ and ‘high fat diet and obesity’ with the filters ‘other animals’ and ‘publication dates’) revealed that 416 000 animal-based HFD studies have been published to date since the first article appeared on PubMed in 1964. The trend for animal-based HFD studies has increased tremendously since then—of the 16 000 papers, >9800 papers were published in the past decade.”)

PO’s criticism of the Petitioner’s invalidity arguments based on select review articles misses the point. The proper legal inquiry under 35 U.S.C. §103 is whether there is a motivation to combine/modify the prior art references and whether there is a reasonable expectation of success. PO does not dispute that using pre-clinical animal studies to launch clinical trials is widely accepted practiced in the field of pharmaceutical research and drug development. PO does not challenge the scientific rigor disclosed in the prior art papers cited in the Petition. PO does not challenge

the research findings cited in the Petition that demonstrate a POSITA would have reasonable expectation of success if the POSITA applies knowledge learned from animal dihydroberberine studies for human treatments. *See* Petition at p. 21 (citing Chen reference in the gastrointestinal disorders field); pp. 23-34 (citing Zhang and Liu references to validate dosage conversion of berberine from animal model to humans in the field of diabetes treatment); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“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.”)

Moreover, PO fails to rebut Grounds 3 and 4 in the Petition. The primary reference relied upon in Grounds 3 and 4 is Zhang – “a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of diabetes.” Ex. 1006 at 2560. One secondary reference in the Petition is Feng, a Nature Scientific Reports article that teaches dihydroberberine is more bioavailable than berberine and can act as a pro-drug for berberine based on, among other things, studies on human cell line models. *See* Ex. 1007 at 2-3. PO’s critique based on the alleged unpredictability of extrapolating rodent diabetes treatment findings to human patients is not relevant and does not refute the obviousness arguments set forth in Grounds 3 and 4 of the Petition.

4. **Discretionary Denial Is Not Warranted Because Material Errors Were Committed by the Patent Office During Patent Examination**

As stated above, discretionary denial of the instant petition is improper because the Patent Office committed material errors during examination of the '961 patent. As a result, it would be appropriate for the Office to use its resources to review such material errors. *See Microsoft Corporation v. Partec Cluster Competence Center GMBH*, IPR2025-00318, Paper 9 at 3 (Director June 12, 2025) (“*Microsoft*”) (finding that “discretionary denial of institution is not warranted” because “Petitioner provides persuasive evidence that the Office erred in a manner material to the patentability of the challenged claims by overlooking the teachings of Budenske and Kambalta, and the combined teachings of Budenske and Lippert, or Budenske and Kambalta with Lippert.”) and that “it is an appropriate use of Office resources to review the potential error”); *Eunsung Global Corp. v. HydraFacial LLC*, IPR2025-00445, Paper 14 at 3 (Director July 10, 2025) (“*Eunsung*”) (finding that “discretionary denial is not appropriate” because “Petitioner persuasively demonstrates that the patent examiner overlooked certain teachings in Karasiuk that appear to disclose the allowable features of the claims”).

During the examination of the application that issued as the '961 Patent, the Applicant amended independent claim 1 by adding a dosage limitation - “wherein the pharmaceutically effective amount of dihydroberberine comprises

approximately 25 mg to approximately 800 mg of dihydroberberine” in response to a 35 U.S.C. §102 rejection by the Examiner based on a Hu reference. *See* Ex. 1002, p. 116. The Applicant argued that “[t]he Hu reference does not teach or suggest at least this [dosage] feature of the claim, as discussed in the Examiner Interview. Instead, the Hu reference teaches the administration of 100mg/kg/day or 2g/kg. (Hu, paragraph 219).” *Id.* at 113. The Examiner Interview Summary record indicates that the Examiner agreed with the Applicant that the added dosage limitation overcomes Hu. *Id.* at 92.

A closer study of Hu’s teachings reveals several material errors the Examiner made. These errors resulted in the erroneous decision by the Patent Office to allow the amended claims to issue.

First, the Examiner overlooked the well-established principle in the field of pharmaceutical science and drug development that dosage translation is *required* to determine an appropriate human dosage based on animal studies. The 100mg/kg/day dosage from Hu cited by the Applicant is an animal dosage. *See* Ex. 1012, p. 20 & ¶ [0219] (“Ten mice per group were used to perform the efficacy study of the compounds. Dihydroberberine derivative 19 or its sulfate salt was mixed into the high-fat diet, and administered at a dose of 100 mg/kg/day for 2 weeks.”) The Examiner failed to apply any dosage translation to evaluate whether Hu would anticipate or render obvious the amended claim reciting the claimed “approximately

25 mg to approximately 800 mg of dihydroberberine” *human* dosage limitation. As explained in the Petition, had the Examiner applied the widely accepted body surface area dosage conversion method, the corresponding human dosage would be approximately 486 mg/day for a 60-kg human subject, which would fall within the “approximately 25 mg to approximately 800 mg” range. In other words, the Examiner would *not* have allowed the amended claim to issue if the Examiner had performed an animal to human dosage translation. *See* Petition at 24-27.

Second, it appears that the Examiner misread Hu as containing teachings on human experiments while what Hu actually teaches are animal studies. This error is reflected in the non-final Office Action where Examiner used 35 U.S.C. §102 as the basis to reject originally filed claim 1, stating the “[Hu] reference discloses methods for managing glucose tolerance and methods for increasing blood ketone levels in an individual by *administering to said individual* dihydroberberine. (See Abstract, pages 1-2, 8 (paragraph [0040], 15-16 (paragraph [0219], and 16-20, and Table 1). These methods read on the instant claim. Since this reference teaches the exact methods, Applicant’s claims are anticipated, and thus, rejected under 35 U.S.C. 102.”). Ex. 1002, pp. 123-24 (emphasis added). However, paragraphs [0040] and [0219] do not teach administering dihydroberberine to human subjects. *See* Ex. 1012, pp. 13, 20. Had the Examiner correctly understood Hu as disclosing experiments on rodent models instead of clinical studies on human subjects, the

Examiner likely would have rejected the claims on §103 grounds. This error apparently preordained the Examiner's later conclusion that the misunderstood "human" dosage (which in fact is an animal dosage) Hu discloses is outside the scope of the claimed human dosage in the amended Claim 1, which resulted in allowance of the amended Claim 1 and all dependent claims.

Third, the Examiner overlooked the Applicant's erroneous representations during the prosecution. Specifically, the Applicant represented that "Hu reference teaches the administration of 100mg/kg/day or 2g/kg. (Hu, paragraph 219)," implying one of the dihydroberberine dosage taught by Hu is 2g/kg. Ex. 1002, p. 113. Hu does not teach such a dosage regime. Instead, the 2g/kg dose is the amount of glucose injected intraperitoneally to the mice to run a glucose tolerance test. Had the Examiner reviewed the "2g/kg" dose disclosure with relevant context in Hu, the Examiner would have had a better appreciation of what Hu teaches and would have found the amended claims obvious over Hu.

Given these material errors, discretionary denial is not warranted.

III. CONCLUSION

For the reasons above, PO's request for discretionary denial should be denied.

DATE: January 2, 2026

Respectfully submitted,

/s/ John Handy

John Handy

Registration No. 68,906

Counsel for Petitioner

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

Under the provisions of 37 C.F.R. § 42.24(d), the undersigned hereby certifies that the foregoing Petitioner's Opposition to Patent Owner's Discretionary Denial Brief contains, as measured by the word-processing system used to prepare this paper, 20 pages. This word count does not include the items excluded by §42.24 as not counting towards the word limit. Interim Director Discretionary Process, <https://www.uspto.gov/patents/ptab/interim-director-discretionary-process>.

DATE: January 2, 2026

Respectfully submitted,

/s/ John Handy _____

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Registration No. 68,906
Counsel for Petitioner

CERTIFICATE OF SERVICE

Pursuant to 37 CFR § 42.105 (b), the undersigned hereby certifies that a copy of this Petitioner's Opposition to Patent Owner's Discretionary Denial has been served on January 2, 2026 upon the following litigation counsel via electronic means:

- Mark Nielsen (mark.nielsen@solidcounsel.com)
- Michael J. Schofield (mike.schofield@solidcounsel.com)

DATE: January 2, 2026

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