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

PETITION FOR *INTER PARTES* REVIEW OF
U.S. PATENT NO. 10,278,961
UNDER 35 U.S.C. §§ 311-319 AND 37 C.F.R. §§ 42.1-100, ET SEQ.

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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")
1011	Aillen JF King, The use of animal models in diabetes research, British Journal of Pharmacology, (2012) 166 877-894. ("King")

No.	Description
1012	U.S. Application 12/443,401, published on May 6, 2010 as US 2010/0113494. ("Hu")

I. INTRODUCTION

Pursuant to 35 U.S.C. §§ 311-319 and 37 C.F.R. § 42.100 *et seq*., Bonerge Lifescience (Hunan) Co., Ltd. ("Bonerge" or "Petitioner") respectfully requests that the Board initiate *inter partes* review ("IPR") of claims 1, 2, 5-7 (the "Challenged Claims") of U.S. Patent No. 10,278,961 (EX1001, the "'961 patent"), owned by Nanjing Nutrabuilding Bio-Tech Co., Ltd. ("Patent Owner"), and seeks a determination that the Challenged Claims be canceled as unpatentable.

II. CHALLENGED CLAIMS AND GROUNDS FOR CHALLENGE

A. The Challenged Claims of the '961 Patent

The Challenged Claims of the '961 patent are reproduced below and in Appendix A for ease of reference:

> 1. A method of managing glucose tolerance in an individual, the method comprising:
> administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.
>
> 2. The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels.
>
> 5. The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.
>
> 6. The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.
>
> 7. The method of claim 1 wherein the dihydroberberine is administered at least once daily.

B. Grounds for Challenge

This Petition, supported by the Expert Declaration of Dr. Ronald J. Shebuski, Sr. (EX1003), requests cancellation of the Challenged Claims on the following grounds:

Ground	Claim(s)	Basis (35 U.S.C. § 103)
Ground 1	1, 2, 5-7	Turner in view of Shaw
Ground 2	5	Turner in view of Shaw and further in view of Zhang
Ground 3	1, 2, 5, 7	Zhang in view of Feng
Ground 4	6	Zhang in View of Feng and further in view of Turner

III. STATEMENT OF REASONS FOR THE RELIEF REQUESTED

A. Summary of the Argument

The Challenged Claims of the ’961 patent are unpatentable as obvious over the prior art references. Claim 1 is directed to a method of “managing glucose tolerance” in an individual by administration of a known compound dihydroberberine at “approximately 25 mg to approximately 800 mg.” Dependent claims 2, 5, 6, and 7 additionally limit the method to “reduc[ing] fasting glucose levels,” “orally administered as a capsule or tablet,” “orally administered as at least one of a food product or beverage product,” and “administered at least once daily,” respectively.

The claimed compound dihydroberberine[1] is a derivative of berberine[2], which is a traditional Chinese medicine ingested for treating diabetes but also known for its low bioavailability. Various clinical studies dated the last 1990s and early 2000s (well before the earliest priority date of the '961 patent) have reported that BBR is effective for reducing blood glucose levels and treating diabetes patients. Meanwhile, preclinical animal studies on dhBBR have shown that the derivative is effective in reducing blood glucose levels in rodents at specific dosage amounts. Studies have also shown that dhBBR is a transient form of BBR in the intestinal lumen with improved physiochemical characteristics for absorption by the intestines.

The method claims at issue therefore are rendered obvious by the vast research done on the efficacy of BBR, and dhBBR as its more bioavailable derivative, including clinical trials, animal studies, and in vitro/in vivo assays. A POSA would have been motivated to try, and would have a reasonable expectation of success, to arrive the claimed dosage amount of "approximately 25 mg to approximately 800

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[1] Dihydroberberine is hereinafter referred to as dhBBR.

[2] Berberine is commonly used in China as a nonprescription oral drug to treat gut infections and diarrheas with few side effects. EX1004 (Turner) at 1414. Berberine is hereinafter referred to as BBR.

mg" of dhBBR, administered orally, for managing human blood glucose levels. A POSA could have arrived at the claimed dosage amount of dhBBR for managing blood glucose levels by using the dhBBR animal studies as the primary reference and applying the well-established body surface area normalization method to start a dosage appropriate for humans. Alternatively, a POSA could have utilized the BBR clinical trial data for treating diabetes as the primary reference and applying the understanding that dhBBR acts as a pro-drug that has an intestine absorption rate higher than that of BBR but is converted back to BBR after absorption in the intestine issues and enters the blood, to arrive at a necessarily lowered dosage amount of dhBBR as a BBR substitute.

B. The '961 Patent, Its Specification and Prosecution History

1. The '961 Patent and Specification

The '961 patent, entitled "Administration of berberine metabolites," is generally directed to methods of administering dihydroberberine to manage blood glucose levels and/or increase blood ketone levels. Ex. 1001, Abstract. DhBBR is a berberine metabolite. *Id*. at 1:44-48. The '961 patent has two independent claims – claims 1 and 9. This Petition challenges the patentability of claim 1 and its dependent claims 2, 5, 6, and 7.

The '961 patent acknowledges as prior art background that (i) BBR is a naturally occurring substance that has been administered to humans in the past, (*id*.

at 1:21-27), (ii) BBR can lower fasting blood glucose if administered at effective amounts, (*id*. at 1:27-33); (iii) BBR has low bioavailability (*id*. at 1:33-40). At the time of the filing of the '961 patent, dhBBR was commercially available. *Id*. at 4:23-25.

The '961 patent claims that it made a novel finding that orally administered dhBBR can lower blood glucose levels but at a much-reduced dosage, and that the improved efficacy of dhBBR compared with BBR is "unexpected." Specifically, the specification makes the following remarks and claims

> The amount of dihydroberberine may be less than the amount of berberine required to achieve the same amount of glucose tolerance (e.g., a predetermined fasting glucose level, a predetermined range of blood glucose, a normal or other blood glucose level as determined by health guidelines, a normal or other fasting blood glucose as determined by health guidelines, etc.). In some implementations, an amount of dihydroberberine may provide the same level of glucose tolerance as at least double the same amount of berberine (e.g., the dihydroberberine may be at least twice as effective as berberine and thus half or less than half of a first amount of dihydroberberine would be required to achieve the same results as the first amount of berberine). This result is unexpected since one would expect berberine and dihydroberberine to have similar properties. Even with the known increase bioavailability of dihydroberberine over berberine, the ability to administer as little as half as much dihydroberberine as berberine to achieve similar results in glucose tolerance is unexpected.

Id. at 4:66-5:18. This finding, the specification claims, would make dhBBR a better diabetes drug because a lower dosage would mean reduced side effects, eased palatability, eased administration, reduced costs, etc. *Id.* at 5:18-27.

Finally, the ’961 patent disclosed data collected from a few experiments to support its claimed findings. *See id*. at 9:10-67 (Examples 1-4). In these experiments, human subjects received various amounts of either BBR or dhBBR. Blood was drawn from the subjects to measure each subject’s blood glucose levels and their changes over time. *Id*. at 9:12-16. The ’961 patent provides limited information about these subjects. *See id.* at 9:10-67. There was no disclosure of the subjects’ age, gender, health conditions, or other demographic information.

2. The ’961 Patent File History

The ’961 patent issued from U.S. Patent Application No. 15/491,933 (“the ’933 Application”), filed April 19, 2017, claiming the benefit of Provisional Application No. 62/324,794, filed on April 19, 2016. *Id.,* cover page.

Applicant filed the ’933 Application with 20 claims and made an amendment withdrawing claim 15 and amending claims 16-20 after the Restriction Requirement. EX1002, Amendment and Reply to Restriction Requirement Mailed December 12, 2017, dated February 5, 2018. The Examiner rejected all pending claims as anticipated by Hu et al. (U.S. Pub. 2010/0113494) in an office action dated May 24, 2018. *Id.,* Office Action dated May 24, 2018. Examiner stated that “[Hu] discloses methods for managing glucose tolerance and methods for increasing blood ketone levels in an individual by administering to said individual dihydroberberine.” *Id.* at page 3.

On November 20, 2018, Applicants had an interview with the Examiner and submitted a response amending independent claims 1 and 10, canceling claim 5, and adding new dependent claims 21-22. *Id.,* Amendment and Reply to Office Action Mailed May 24, 2018, dated November 20, 2018. Specifically, Applicant contended that the added dosage limitation - "wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine" – distinguishes the amended independent claims 1 and 10[3] over the Hu reference. *Id.* at pages 2-3. Hu, according to the Applicant, taught "the administration of 100mg/kg/day or 2g/kg[4]." *Id*. at pg. 7.

There is no record in the prosecution history whether the Applicant and the Examiner discussed how to convert the dosage disclosed Hu's rodent model for application to humans, and whether such a conversion would render the amended claims of the '933 Application obvious. The examiner allowed the amended claims on December 26, 2018. *Id.* Notice of Allowance. The '961 patent issued on May 7, 2019.

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[3] They matured into Claims 1 and 9 of the issued '961 Patent.

[4] Hu disclosed injecting glucose intraperitoneally to mice at a dose of 2 g/kg of the mice's body weight as part of the set up for the animal study. EX1012 at ¶0219. Hu did not disclose administering a 2 g/kg dosage of dhBBR to the lab mice.

C. Level of Ordinary Skill in the Art

A person of ordinary skill in the art ("POSA") as of April 19, 2016 (the filing date of Provisional Application No. 62/324,794) or April 19, 2017 (the filing date of Application No. 15/491,933) with respect to the '961 patent would be a researcher engaged in developing pharmaceutical formulation, preclinical and clinical drug development including selecting and evaluating pharmaceutically effective amounts of active substances. EX1003, ¶27. A POSA would have had the general knowledge in pharmacology, drug metabolism, pharmacokinetics, pharmacodynamics, and toxicology. Furthermore, the POSA would be expected to have knowledge and considerable experience in what is known in the field as "ADME" (**A**bsorption, **D**istribution, **M**etabolism, and **E**xcretion The researcher should preferably have advanced pharmaceutical sciences degree such as Ph.D. or Pharm. D. *Id*. Alternatively, the researcher should have a master's degree preferably a PhD in Pharmacology/Toxicology, Pharmaceutics, or Medicinal Chemistry and several years of experience in pharmaceutical formulation and drug development. *Id*.

D. Claim Construction Under 37 C.F.R. § 42.104(b)(3)

The Challenged Claims are interpreted using the same claim construction standard used to construe claims in a civil action in federal district court, namely the *Phillips* standard. 37 C.F.R. § 42.100(b); *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

For purposes of this proceeding only, Petitioner contends that, except for the claim term "reduces fasting glucose levels," no formal claim construction is necessary because the Challenged Claims are invalid under their plain and ordinary meanings, and "claim terms need only be construed 'to the extent necessary to resolve the controversy.'" *Wellman, Inc. v. Eastman Chem. Co.*, 642 F.3d 1355, 1361 (Fed. Cir. 2011) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng'g, Inc.,* 200 F.3d 795, 803 (Fed. Cir. 1999)).

Independent claim 1 recites "a method for managing glucose tolerance" in the preamble. EX1001, 11:28. This phrase should carry their respective ordinary meanings. The '961 patent sets forth "managing glucose tolerance" to include "decrease and/or maintain blood glucose level, decrease and/or maintain fasting blood glucose, increase ability to process glucose, etc." *Id.* at 2:20-23.

Dependent claim 6 recites "dihydroberberine is orally administered as at least one of a food product or beverage product." The term "food product" should carry its ordinary meaning. The '961 patent discloses the following regarding how the dihydroberberine may be orally administered as a food product. *Id.* at 10:6-18 ("In some implementations, the described composition may be administered via tablet, capsule, powdered supplement; ready-to-drink formulation; topical product including transdermals; cosmeceutical product; foods such bars, cookies, gum, candy, functional foods; toothpaste, sublingual product; injection; intravenous

fluids; beverages such as shots or energy shots; inhalers; sublinguals; and/or combinations thereof. The described composition may be provided in a powdered form that allows the described composition to be sprinkled on food, mixed with a liquid to provide a beverage, directly administered."); 8:21-24 ("In some implementations, the composition may be provided in a delivery form such powder (e.g., that capable consumed separately, mixed with drinks, and/or food) and/or tablet.").

1. Claim Construction for Claim 2 reciting "the administration of dihydroberberine reduces fasting glucose levels"

Dependent claim 2 recites "reduces fasting glucose levels."

The '961 patent specification discloses four experimental studies – Examples 1 through 4. *Id*. at 9:8-67; Figs. 1-4. The effect of dihydroberberine on "fasting glucose levels," as taught by these experiments, is explained in a single sentence that comments on the results from Example 1 – "an unexpected result of the administration of dihydroberberine is that administration of dihydroberberine may keep blood glucose levels closer *to fasting blood glucose* than berberine." *Id*. at 9:22-25 (emphasis added).

All four experimental studies disclosed in the '961 specification comprise of "glucose challenge tests" studies on human subjects after they were administered varying doses of BBR or dhBBR or compositions containing the same. EX1003 at ¶¶32-33; EX1001 at 9:8-67. A "glucose challenge tests" tracks changes in a subject's

blood glucose levels within hours of receiving a sugar shot. EX1003 at ¶33. The ’961 specification teaches administering 75 grams of glucose to the testing subjects; it does not disclose how the glucose is taken by the subjects. EX1001 at 9:8-67. For the first study (Example 1), the “glucose challenge tests” records five subjects’ blood glucose levels at time zero (before 75 grams of glucose were administered) and at 30, 60, 120, and 180 minutes post glucose administration. EX1003 at ¶34; EX1001 at 9:12-19. Three separate “glucose challenge tests” were performed on each subject. *Id*. The blood glucose levels were measured and averaged for analysis. *Id*.

Given the only disclosure from the ’961 patent experiments supporting the claim 2 limitation is the observation from the first glucose challenge test study that “administration of dihydroberberine may keep blood glucose levels closer to fasting blood glucose than berberine,” claim 2 would be satisfied if a prior art reference (or a combination of prior art references) demonstrates via a glucose challenge test or similar type of glucose tolerance tests where the administration of dhBBR would keep blood glucose levels closer to fasting blood glucose levels than BBR would. EX1003 at ¶35.

E. The Scope and Content of the Prior Art

The ’961 patent issued from the ’933 Application. The application claimed the benefit of Provisional Application No. 62/324,794, filed on April 19, 2016. *Id.,* cover page. Solely for purposes of evaluating prior art in this proceeding, this

Petition will treat April 19, 2016, as the earliest effective filing date of the '961 patent and may refer to the same as "the priority date" or "the time of the alleged invention" without conceding the propriety of the priority claim. As further discussed below, each of the references on which this Petition relies was published in or before 2015 and therefore qualifies as prior art to the '961 patent under AIA 35 U.S.C. § 102(a)(1).

These prior art references are briefly discussed below.

1. Turner

Turner was published on May 2008 and therefore constitutes prior art under AIA 35 U.S.C. § 102(a)(1).

Turner is entitled "Berberine and Its More Biologically Available Derivative Dihydroberberine, Inhibit Mitochondrial Respiratory Complex I." EX1004 at 1414. The authors of Turner "explored whether derivatization of BBR could improve its in vivo efficacy" and conducted studies to examine the effect of dhBBR "on … glucose metabolism in rodents fed a high-fat diet." *Id.* Among other results, Turner found that dhBBR "displayed improved in vivo efficacy in terms of counteracting … insulin resistance in high-fat-fed rodents. This effect is likely due to enhanced oral bioavailability." *Id*. Turner concluded that "dhBBR represents an attractive potential therapy for the treatment of type 2 diabetes and other components of the metabolic syndrome." *Id*. at 1417.

Specifically, Turner noted that they had previously "reported that berberine (BBR) displays insulin-sensitizing properties in rodent models of insulin resistance and diabetes" yet "considerably large oral doses … of BBR were required for beneficial metabolic effects in rodents." *Id*. at 1414; *see also id.* at 1417 ("A potential disadvantage of BBR as an in vivo compound for treatment of diabetes is that we and others have previously reported the need for relatively high doses in rodents to achieve beneficial metabolic effects.") As such, Turner designed a number of BBR derivatives and conducted rodent studies, "[a]iming to improve [BBR's] therapeutic efficacy." *Id*. at 1414.

Turner discovered that dhBBR has improved *in vivo* efficacy compared with BBR because of these experimental observations:

> At 100 mg · kg^{-1} · day^{-1}, dhBBR reduced adiposity and improved glucose tolerance in HFD mice, whereas we observed no effects of BBR at this dose. Furthermore, in HFD rats, the beneficial effects of dhBBR at 100 mg · kg^{-1} · day^{-1} were of a similar magnitude to those previously reported for 380 mg · kg^{-1} · day^{-1} of BBR.

Id. at 1417. These observations were based on the rodent study results published in the article. *See id*. at Fig. 3 and Table 1 (and corresponding text).

Finaly, Turner predicted that dhBBR would have improved efficacy due to enhanced oral bioavailability because BBR "possesses an extremely flat configuration, which is likely to have limited absorption across the intestinal epithelia" while "derivatization to dhBBR was predicted to open up the structure,

making it more amenable to uptake." *Id*. at 1417. Turner noted that the "pharmokinetics data were consistent with this prediction, with dhBBR displaying improved absorption compared with BBR." *Id*. (emphasis added). Finally, Turner noted that BBR is likely the active moiety for treating diabetes and dhBBR acts as an effective vehicle for delivering BBR to the circulation because the data revealed "that once absorbed, dhBBR was rapidly converted back to BBR." *Id*.

2. Shaw

Shaw was published in March 2007 and therefore constitutes prior art under AIA 35 U.S.C. § 102(a)(1).

Shaw is entitled "Dose translation from animal to huma studies revisited." EX1005 at Title. Shaw explained how to use the body surface area (BSA) normalization method to translate drug dosage from animals to humans. Shaw disclosed the BSA conversation formula and included a conversation table based on the BSA method. *Id*. at 660.

Formula for Dose Translation Based on BSA
$\text{HED (mg/kg)} = \text{Animal dose (mg/kg)}$ *multiplied by* $\frac{\text{Animal } Km}{\text{Human } Km}$

Shaw noted that "BSA-based dose calculation is the most appropriate method and is far superior to the simple conversion based on body weight." *Id*. at 661. Shaw

advocated the use of BSA method when "converting a dose for translation from animals to humans." *Id*. at Abstract.

3. Feng

Feng was published on July 15, 2015 and therefore constitutes prior art under AIA 35 U.S.C. § 102(a)(1).

Feng is entitled "Transforming berberine into its intestine-absorbable form by the gut microbiota." EX1007 at 1. Feng set out to study the "absorption mechanism" of berberine because BBR exhibits poor solubility. *Id.* at 1 (Abstract). Based on both in vitro and in vivo studies, Feng concluded that "the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." *Id.*

Specifically, Feng acknowledged that BBR was known for treating type 2 diabetes and that BBR has "poor water solubility and is presumably very difficult for intestinal epithelial cells to absorb." *Id*. at 2. Feng first detected dhBBR as a metabolite in the intestines of rodents on a BBR diet. *Id*. at Fig. 1(c). Feng performed additional in vitro studies where BBR was incubated with bacteria isolated from rodent intestines as well as bacteria isolated from human intestines. *See id*. at 2-3, Fig. 1(d). The results confirmed that the bacterial from the guts converted BBR to dhBBR. *Id*. Feng then performed in vitro studies using the Caco-2 cell line (a widely used human intestinal epithelial cell model) to examine how dhBBR

compares with BBR in terms of the rate of absorption by the intestines. *See id*. at Fig. 3(a). Feng also administered dhBBR and/or BBR to rats and used concentration-time curve studies to examine how the rates of absorption compare. *See id*. at Fig. 3(b)-3(d). Both the *in vivo* and *in vitro* studies confirm that dhBBR has an intestinal absorption rate higher than that of BBR. The authors conclude the data shows that dhBBR "has an intestinal absorption rate 5-fold that of BBR in animals." *Id*. at 1. Interestingly, however, the authors found that dhBBR gets reverted to BBR via oxidization soon after dhBBR enters the intestine tissues. *Id.* at 6-7. The authors concluded that "dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption." *Id.* at 8.

Based on the author's various studies, Feng proposed the mechanism of absorption of BBR in the intestine and the role of dhBBR in Figure 6. *Id.* at Fig. 6.

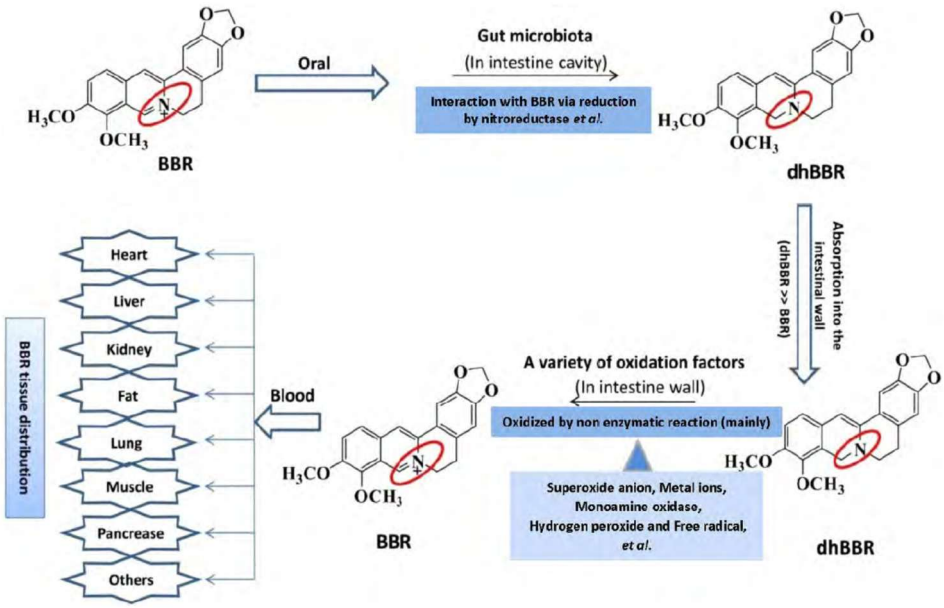

Figure 6. Proposed mechanism of BBR absorption in the intestine.

4. Zhang

Zhang was published in July 2008 and therefore constitutes prior art under AIA 35 U.S.C. § 102(a)(1).

Zhang is entitled "Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine." EX1006 at Title. Zhang disclosed a study designed to "evaluate the efficacy and safety of berberine in the treatment of type 2 diabetic patients with dyslipidemia." *Id*. at 2559. Based on their studies, Zhang concluded that berberine is effective and safe in the treatment of type 2 diabetes. *Id*. Zhang acknowledged that there were many reported clinical investigations of berberine for treating diabetes before 2008. *Id*. at 2560. Zhang set out, on the other hand, to perform "a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of diabetes and dyslipidemia." *Id*. Specifically, Zhang's studies involved orally administering 500mg of berberine twice a day to randomized patients across multiple hospitals. *Id*. The results showed that patients receiving berberine at the 1,000 mg a day dosage "had a significant improvement in fasting plasma glucose" as compared with patients who received placebo. *Id*. at 2561.

IV. GROUND 1: CLAIMS 1, 2, 5, 6, AND 7 ARE RENDERED OBVIOUS BY TURNER IN VIEW OF SHAW

The law is well established that "obviousness does not require absolute predictability of success. . . . All that is required is a reasonable expectation of

success." *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). "[O]bviousness 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). "[W]here a method claim merely confirms a result in humans based on what was observed and predicted from animal testing, the claim is obvious." *Bone Care Int'l, L.L.C. v. Roxane Labs., Inc*., No. 09-cv-285 (GMS), at *151 (D. Del. June 11, 2012)

A. Claim 1 Is Obvious

1. Turner discloses that dhBBR is effective for managing glucose tolerance in rodents and opines that dhBBR can be effective for human diabetes treatment.

As explained above, Turner discovered that dhBBR, a BBR derivative, has improved in vivo efficacy compared with BBR for managing blood glucose tolerance in animal studies. Turner discovered that dhBBR, a BBR derivative, has improved *in vivo* efficacy compared with BBR for managing blood glucose tolerance in animal studies. Specifically, Turner subjected rodents on a high-fat-diet[5] (HFD) to glucose tolerance tests where one group of mice were fed dhBBR for the final two

[5] The HFD diet was introduced to generates insulin resistance in animal. EX1004 (Turner) at 1415.

weeks of feeding, and the other group were fed BBR. EX1004 at 1415. The administered dosage for both dhBBR and BBR is 100 mg/kg/day. *Id*. Blood was drawn from the subject mice to measure the blood glucose levels and their changes over time. The results were plotted and disclosed in Fig. 3(B). This *in vivo* animal study demonstrated that dhBBR has improved efficacy for managing glucose tolerance. *See id*. at 1415-16 ("In mice fed an HFD, treatment with dhBBR … markedly reduced adiposity and improved glucose tolerance, compared with HFD controls (Fig. 3). At the same dose, BBR had no effect on adiposity or glucose tolerance (Fig. 3), whereas at a dose of 560 mg. kg-1.day-1 (data not shown), we observed the expected effects of BBR."). Based on these animal studies, Turner opined that dhBBR is "an attractive potential therapy for the treatment of type 2 diabetes and other components of the metabolic syndrome." *Id*. at 1417. A POSA would find it obvious to study dhBBR's efficacy for managing human glucose tolerance through clinical studies. EX1003, ¶44.

2. <u>A POSA would be motivated to administer dhBBR for managing glucose tolerance in humans with reasonable expectation of success.</u>

Turner opined that dhBBR would be an effective drug for managing glucose tolerance in humans with reasonable expectations of success because the studies in Turner were conducted on one of the most commonly used animal models for type 2 diabetes research. EX1004 at 1417.

More importantly, a POSA is expected to use findings from pre-clinical animal studies as theoretical foundations and experimental evidence to launch clinical studies and applications of a new drug. EX1003, ¶45. A POSA understands that high-fat diet mice model is one of the most common animal models to research type 2 diabetes, especially for treatments to improve insulin resistance. EX1003, ¶46; EX1011 (King) at 881-882 (outlining some of "the most commonly used models for type 2 diabetes" in Table 2) & Table 2.[6] King described an animal model where the C57BL/6 mice were fed high-fat diet preferrable for several weeks to induce more pronounced weight gains. *Id*. at 883. King further commented that the HFD animal model "is thought to model the human [type 2 diabetes] situation more accurately than genetic models of obesity-induced diabetes." *Id*. at 884. The studies in Turner followed the same HFD animal model that King described for type 2 diabetes. The animal models used in Turner's diabetes study are obese mice induced by high fat feeding. EX1004 (Turner) at 1415 & Fig. 3. The mouse strain used in Turner is C57BL/6J. The mice were fed high-fat diet for ten weeks to induce obesity before administration of BBR or dhBBR to study their therapeutic efficacy. *Id*.

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[6] King was published in early 2012, well before the earliest priority date (4/19/2016) of the '961 patent. King is entitled "The use of animal models in diabetes research." Ex. 1011, Title.

Indeed, researchers in the berberine field already relied on rodent studies to launch clinical studies that yielded successes. *See* EX1003, ¶47; EX1009 (Chen)[7] at 1822-23 (findings from rodent studies of berberine's effect on gastrointestinal disorders provided "a theoretical foundation and experimental evidence for berberine's clinical application in treating GI disorders" and concluding based on the author's clinical studies that a berberine derivative can reduce patient with irritable bowel syndrome and improve their quality of life).

[7] Chen was published in late 2015, well before the earliest priority date of the '691 patent. Chen is entitled "A randomized clinical trial of berberine hydrochloride in patients with diarrhea-predominant irritable bowel syndrome." EX1009 at Title. Chen cited a number of animal studies of berberine's effects on gastrointestinal disorders using rodent models. *Id*. at 1822. Using these rodent study findings as "theoretical foundation and experimental evidence," (*id*. at 1822), Chen performed clinical trials of berberine hydrochloride in patients with irritable bowel syndrome and concluded that berberine hydrochloride is "well tolerated and reduces IBS-D symptoms, which effectively improved patients" quality of life. *Id*. at Abstract.

3. A POSA would have experimented with a human equivalent dosage (HED) amount of dhBBR using the Body Service Area (BSA) method for managing blood glucose levels and would have a reasonable expectation of success.

As explained in Shaw, the body surface area (BSA) normalization method is the "most appropriate" method to translate drug doses from animal studies to human studies. EX1005 at 661. Using BSA method for converting drug doses from animal studies to clinical trials is well known by a POSA as it is also recommended by the FDA Guideline document[8]. EX1003 at ¶48; EX1008 (FDA Guidance) at 6 ("normalization to body surface area has remained a widespread practice for estimating an HED[9] based on an animal dose."). The FDA Guideline suggests that a pharmacologically active Human Equivalent Dosage of a new drug can "be derived from a PAD[10] estimate by using a BSA-CF[11]" based on in vivo animal studies. *Id.* at 12.

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[8] FDA Guidance was published in July 2005 and well before the earliest filing date of the '961 patent. FDA Guidance is entitled "Guidance for Industry Estimating the Maximum Safe Starting Dose in Initial Clinical Trials for Therapeutics in Adult Healthy Volunteers." EX1008 at Title.

[9] HED is short for "Human Equivalent Dose." EX1008 at 1.

[10] PAD is short for "pharmacologically active dose." EX1008 at 4.

[11] BSA-CF is short for "body surface area conversion factor." EX1008 at 3.

Moreover, the validity of the BSA method for dosage conversion specifically with respect to berberine (and its derivatives) for treating diabetes can be verified by studies done by researchers in this field at the relevant time period. EX1003, ¶¶49-51. For example, the authors of Zhang conducted clinical studies demonstrating that a daily dosage of 1.0 gram of berberine is effective in reducing fasting blood glucose levels in type 2 diabetic patients. EX1006 at 2559; EX1003, ¶50. The authors of Liu[12] conducted rodent studies and demonstrated that a daily dosage of 200mg/kg of berberine administered to diabetic rats for five weeks is effective in reducing fasting blood glucose levels. EX1010 at 372, 374 & Fig. 1(b); EX1003, ¶51.

Using the BSA conversion formula disclosed in Shaw, the HED of a 200mg/kg/day dosage administered to rats is approximately 16.2 mg/kg/day, or 980 mg/day (based on an average human weight of 60kg). Because the HED dosage converted from the Liu rodent studies (972 mg/day) approximates the

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[12] Liu was published on March 13, 2010, well before the earliest priority date of the '961 patent. Liu is entitled "Berberine suppresses intestinal disaccharidases with beneficial metabolic effects in diabetic states, evidences from in vivo and in vitro study." EX1010 at Title. At a daily dosage level of 200 mg/kg of berberine, Liu teaches that "significantly decreased the fasting blood glucose levels" in rats that were induced by STZ to have diabetic symptoms. *See id*. at 374 & Fig. 1(b).

pharmaceutically effective BBR dosage disclosed in the Zhang clinical studies (1000 mg/day), a POSA would have understood that the BSA normalization method is validated for diabetic research on the therapeutic effects of berberine (or its derivative). EX1003, ¶52.

4. A BSA conversion of the Turner rodent dosage amount falls within the recited Human Dosage Range in the '961 Patent and the converted dosage amount would have a reasonable expectation of success.

Applying the BSA conversion method as taught in Shaw to the dosage amount disclosed in Turner, a POSA can predict, with reasonable expectation of success, that the pharmaceutically effective dosage amount of dhBBR for application to humans is approximately 8.1 mg/kg/day, or 486 mg/day (based on an average human weight of 60 kg.) EX1003, ¶53.

Specially, Shaw disclosed the BSA conversation formula where HED is calculated from the animal dosage multiplied by animal *Km* and divided by Human *Km*. EX1005 at 660. The Km value for mouse is 3. *Id* at Table 1. The Km value for an adult human is 37. *Id*. The dosage amount disclosed in Turner that is effective in managing blood glucose is 100mg/kg/day for mice. EX1004 at 1415-16. The HED value is therefore approximately 8.1 mg/kg/day = 100mg·kg/day/*3/37, i.e., a 486 mg/day dosage (for an average human adult weighing about 60 kg), which falls within the "approximately 25 mg to approximately 800 mg" dosage range recited in Claim 1 of the '691 patent. EX1003, ¶53. *See In re Peterson*, 315 F.3d 1325, 1329

(Fed. Cir. 2003) ("A *prima facie* case of obviousness typically exists when the ranges of a claimed composition overlap the ranges disclosed in the prior art.").

The reasonable expectation of success of using the BSA conversion can be corroborated by using the BSA conversion method disclosed in Table 1 from the FDA Guidance, which yields approximately the same HED dosage amount. EX1003, ¶¶54-57.

FDA Guidance recommended a standardized process for selecting the maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities in adult healthy volunteers. EX1008 at 1. According to the guidance, this process "pertains primarily to drug products for which systemic exposure is intended; it does not address dose escalation or maximum allowable doses in clinical trials." *Id*. at 2. Specifically, part of the process involves extrapolating NOAEL (no observed adverse effect levels) dosage data derived from animal toxicity studies to a HED dosage. FDA Guidance further teaches that "normalization to body surface area has remained a widespread practice for estimating an HED based on an animal dose." *Id*. at 6. The process involves further applying a safety factor to the HED to "increase assurance that the first dose in humans will not cause adverse effects." *Id*. at 4. The default safety factor is 10. *Id*. at 10. FDA Guidance also advises clinicians to consider the pharmacologically active dose as part of MRSD evaluation. *Id*. at 12. FDA Guidance acknowledges

that selection of a PAD (pharmacologically active dose) is outside the scope of the guidance but nevertheless discloses that it is appropriate to derive a HED dosage from in vivo PAD studies using the BSA-CF method. *Id*. at 12. EX1003, ¶55.

FDA Guidance disclosed the BSA conversation formula where HED (measured in mg/kg) is calculated by dividing the animal dosage (also measured in mg/kg) by a predetermined conversion factor. EX1008 at 7 & Table 1. The conversion factor for mice is 12.3. *Id* at Table 1. The mice dosage amount disclosed in Turner that is effective in managing blood glucose is 100mg/kg/day. EX1004 at 1415-16; EX1003 at ¶39. The HED value is therefore approximately 8.1 mg/kg/day = 100mg/kg/day divided by 12.3. For an average human adult weighing about 60 kg, the 8.1 mg/kg/day translates to about 486 mg/day, which falls within the "approximately 25 mg to approximately 800 mg" dosage range recited in Claim 1 of the '691 patent. EX1003, ¶56; *see In re Peterson*, 315 at 1329.

The FDA Guidance recommends applying an additional default safety factor of 10 for selecting the maximum recommended starting dosage for first-in-human trial to "increase assurance that the first dose in humans will not cause adverse effects." EX1008 at 4. A POSA would have understood that the pharmacologically active HED of the dhBBR is likely greater than the recommended maximum recommended *starting* dosage. EX1003, ¶ 57. A POSA may further predict that the HED at 486 mg/day of dhBBR derived from the BSA-normalization method is a

pharmaceutically effective dosage. *Id*. Regardless, even applying the default safety factor of 10, the maximum recommended starting dosage for an average human adult weighing about 60 kg is approximately 49 mg/day (486 mg/day divided by 10) and still falls within the "approximately 25 mg to approximately 800 mg" dosage range recited in Claim 1 of the '691 patent. *Id*.; *see In re Peterson*, 315 at 1329.

5. Invalidity Claim Chart for Claim 1

Provided below is an invalidity claim chart for Claim 1 summarizing the above analysis.

Claim 1	Claim 1 is rendered obvious by Turner in view of Shaw
A method of managing glucose tolerance in an individual, the method comprising:	To the extent the preamble is limiting, Turner teaches a method of managing glucose tolerance in rodent models. EX1003, ¶37. • "The effect of a BBR derivative, dihydroberberine (dhBBR), on … glucose metabolism was examined in rodents fed a high-fat diet." EX1004 at 1414. • "a novel BBR derivative, dhBBR, was identified that displayed improved in vivo efficacy in terms of counteracting … insulin resistance in high-fat–fed rodents." *Id*. at 1414. • "In mice fed an HFD, treatment with dhBBR …

	markedly … improved glucose tolerance, compared with HFD controls (Fig. 3)." *Id.* at 1415. Turner discloses potentially conducting clinical studies of dhBBR for managing glucose tolerance in humans. EX1003, ¶38. • "dhBBR represents an attractive potential therapy for the treatment of type 2 diabetes and other components of the metabolic syndrome." EX1004 at 1417.
administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to	Turner discloses potentially conducting clinical studies of dhBBR for managing glucose tolerance in humans. EX1003, ¶ 38. • "The effect of a BBR derivative, dihydroberberine (dhBBR), on … glucose metabolism was examined in rodents fed a high-fat diet." EX1004 at 1414. • "dhBBR represents an attractive potential therapy for the treatment of type 2 diabetes and other components of the metabolic syndrome." *Id*. at 1417. Turner also teaches that a dosage amount of

approximately 800 mg of dihydroberberine.	100mg/kg/day is pharmaceutically effective for managing glucose tolerance in rodents. EX1003, ¶ 39. • "a novel BBR derivative, dhBBR, was identified that displayed improved in vivo efficacy in terms of counteracting … insulin resistance in high-fat–fed rodents." EX1004 at 1414. • "In mice fed an HFD, treatment with dhBBR ($100mg{\cdot}kg^{-1}{\cdot}day^{-1}$) markedly … improved glucose tolerance, compared with HFD controls (Fig. 3)." *Id.* at 1415. The BSA conversion of the pharmaceutically effective rodent dosage amount disclosed in Turner to pharmaceutically effective human dosage falls within the recited "approximately 25 mg to approximately 800 mg" dosage range. EX1003, ¶¶ 40-43. • "In mice fed an HFD, treatment with dhBBR ($100mg{\cdot}kg^{-1}{\cdot}day^{-1}$) markedly … improved glucose tolerance, compared with HFD controls (Fig. 3)." EX1004 at 1415.

	• Under Shaw, HED (mg/kg) = Animal dose (mg/kg) * Animal Km / Human Km. EX1005 at 660. • Km factor for adult human is 37; Km factor for mouse is 3. *Id*. at 660. • The converted HED under Shaw is approximately 8.1 mg/kg/·day i.e., a 486 mg/day dosage (for an average human adult weighing about 60 kg). A POSA would have a reasonable expectation of success with this dosage. *See supra* at IV.A.1-4. First, A POSA would be motivated to administer dhBBR to humans for managing glucose tolerance with reasonable expectation of success. *See* EX1003 at ¶¶44-47; EX1004 (Turner) at 1417; EX1011 (King) at 884; EX1009 (Chen) at 1822-23, and *supra* at IV.A.2. Second, a POSA would be motivated to use Body Service Area normalization method to start the clinical trial of a pharmaceutically effective dhBBR dosage amount for humans based on the Turner rodent studies. EX1003 at ¶¶48-57. *See supra* at IV.A.3. *See also*

	• "Currently, BSA-based dose calculation is the most appropriate method and is far superior to the simple conversion based on body weight." EX1005 (Shaw) at 661. • "We advocate the use of BSA as a factor when converting a dose for translation from animals to humans, especially for phase I and phase II clinical trials." EX1005 (Shaw) at Abstract. • "normalization to body surface area has remained a widespread practice for estimating an HED based on an animal dose." EX1008 (FDA Guidance) at 6. • A POSA would have reasonable expectation of success because the validity of the BSA method for dosage conversion specifically with respect to berberine (and its derivatives) for treating diabetes can be verified by studies done by researchers in this field at the relevant time period such as comparing prior art references Zhang with Liu. EX1003 at ¶¶49-52; *See supra* at IV.A.3-4.

	• A POSA's reasonable expectation of success can be corroborated by similar conversion following FDA Guidance. EX1003 at ¶¶54-57.
	  o Under FDA Guidance, HED (mg/kg) = Animal dose (mg/kg) divided by a conversion factor. EX1008 (FDA Guidance) at 7 & Table 1.
	  o The conversion factor for mouse is 12.3. EX1008 (FDA Guidance) at 7 & Table 1.
	The converted HED under FDA Guidance is approximately 8.1 mg/kg/day *i.e.*, a 486 mg/day dosage (for an average human adult weighing about 60 kg). EX1003 at ¶56; *See supra* at IV.A.4.

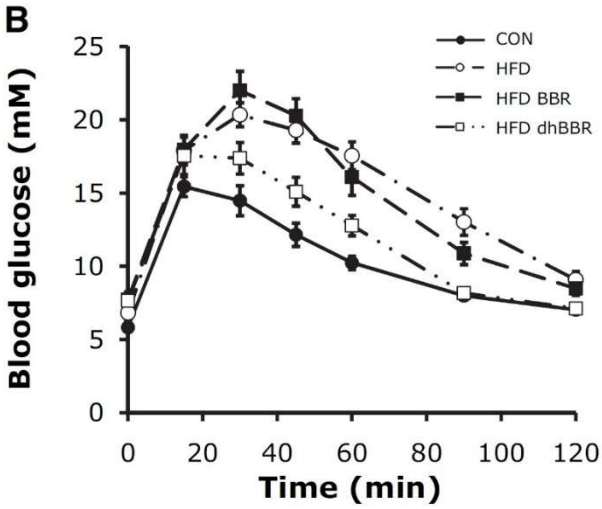
B. Claims 2, 5, 6, and 7 Are Obvious

Provided below are invalidity claim charts for claims 2, 5, 6, and 7.

Claim 2	Claim 2 is rendered obvious by Turner in view of Shaw
The method of claim 1 wherein the administration of	A POSA would have understood that claim 2 is satisfied by Tuner in view of Shaw because Turner demonstrates, via a glucose tolerance test, that administration of

dihydroberberine reduces fasting glucose levels.[13]	dihydroberberine would keep mice's blood glucose levels closer to fasting blood glucose levels than berberine. EX1003, ¶¶ 58-60; EX1004 at Figs. 3(B) and 3(C). Fig. 3(B) records the mice's blood glucose levels at time zero (before administering 2g/kg of glucose) and at 20, 40, 60, 80, 100, and 120 minutes post glucose administration. The blood glucose levels of mice fed with the HFD/dhBBR diet at a 100 mg/kg/day dosage is closer to the fasting blood glucose levels of the control animals that were not fed a high fat diet. *See* EX1004 at

[13] While the Petitioner understands that it may not challenge the claim languages for lack of enablement or indefiniteness, the Petitioner nevertheless takes note that the '961 patent does not provide any experimental results showing that dhBBR reduced the fasting glucose levels of the human subjects it tested. The only mention of "fasting glucose" in connection with the experimental examples is the following sentence – "In addition, an unexpected result of the administration of dihydroberberine is that administration of dihydroberberine may keep blood glucose levels closer *to fasting blood glucose* than berberine." Ex. 1001 at 9:22-25.

	Fig. 3(B) reproduced below.  BBR is not as effective at reducing the blood glucose levels close to the fasting blood glucose level at the same dosage (100 mg/kg/day) in animals fed a high fat diet in this glucose tolerance test study. Similarly, Fig. 3(C) shows that blood glucose area under the curve is significantly reduced by dhBBR, similar to control animals that were not fed a high fat diet. BBR on the other hand is not effective at reducing blood glucose levels at the prescribed dosage (100 mg/kg/day) in animals fed a high fat diet in this experiment. *See* EX1004 at Fig. 3(C). For reasons stated in *supra* at IV.A.1-4, a POSA would

	have been motivated to combine Turner with Shaw, and would have a reasonable expectation that administering dhBBR to humans would achieve the same success in humans, i.e., the administration of dhBBR would keep blood glucose levels of humans closer to fasting blood glucose levels than berberine, which can be demonstrated via a glucose challenge test. EX1003, ¶61.

Claim 5	Claim 5 is rendered obvious by Turner in view of Shaw.
The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Turner teaches that dihydroberberine can be synthesized and kept in a dry and solid form. EX1003 at ¶63. • EX1004 ("the filter cake was dried overnight to give dihydroberberine sulfate [5,6-Dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium sulfate] (2.9 g, yield 75%)." Turner teaches that BBR is administered orally. EX1003 at ¶62. EX1004 at 1414 ("BBR is commonly used as a nonprescription oral drug in China to treat gut infections

	and diarrhea with few side effects, and its therapeutic potential for the treatment of diabetes … in humans has been reported." Turner teaches that the dihydroberberine is also administered orally because it discloses that dhBBR is administered to the mice the same way BBR is administered, i.e. orally along with the HFD. EX1003 at ¶63. • "Mice and rats were fed for 10 weeks and 4 weeks, respectively, and based on pilot testing for dhBBR in mice, BBR and dhBBR were provided in the HFD at a dose of 100 mg · kg^{-1} · day^{-1} for the final 2 weeks of feeding." EX1004 at 1415. A POSA would have been motivated to administer dhBBR orally to humans because it is customary in the pharmaceutical field to administer the same medicine (e.g., dhBBR) to humans through the same route (p.o., i.e. per oral) used in preclinical animal studies that demonstrate safety and efficacy. EX1003, ¶¶62-64. In fact, various prior art already teach administering BBR

	or its derivatives orally, whether it is an animal study or a clinical trial. EX1003, ¶64; *see*, *e.g.*, EX1004 (Turner) (orally administration of BBR or dhBBR via mixing with HFD diet to rodents); EX1006 (Zhang) (oral administration of BBR as tablets to patients); EX1009 (Chen) (oral administration of berberine hydrochloride to patients); EX1010 (Liu) (oral administration of berberine to diabetic rats). A POSA would have been further motivated to administer dhBBR as a capsule or tablet because dhBBR takes a dry and solid form. EX1003, ¶64. Administering dhBBR as a tablet would also be obvious to a POSA because it is one of the few well known and common forms for administering solid medications orally. *Id*.

Claim 6	Claim 6 is rendered obvious by Turner in view of Shaw.
The method of claim 1 wherein the	Turner teaches that BBR is administered orally to humans. EX1003 at ¶65, EX1004 at 1414 ("BBR is

dihydroberberine is orally administered as at least one of a food product or beverage product.	commonly used as a nonprescription oral drug in China to treat gut infections and diarrhea with few side effects, and its therapeutic potential for the treatment of diabetes … in humans has been reported.”) Turner teaches that dihydroberberine can be synthesized and kept in a dry and solid form. EX1003 at ¶66. • EX1004¸ Supplementary Methods, Preparation of Dihydroberberine (“the filter cake was dried overnight to give dihydroberberine sulfate [5,6-Dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium sulfate] (2.9 g, yield 75%).” Turner teaches that the dihydroberberine is administered orally as mixed with the diet food because it discloses that dhBBR is administered to the mice the same way BBR is administered in the HFD diet. EX1003 at ¶67. • “Mice and rats were fed for 10 weeks and 4 weeks, respectively, and based on pilot testing for dhBBR

	in mice, BBR and dhBBR were provided in the HFD at a dose of 100 mg · kg^{-1} · day^{-1} for the final 2 weeks of feeding." EX1004 at 1415. Because a POSA would understand that the dhBBR was mixed with the mice's chow diet, Turner teaches that dhBBR is orally administered to the mice "as at least one of a food product." EX1003, ¶67. A POSA would have been motivated to administer dhBBR orally to humans because a POSA would have a reasonable expectation of success where the same medicine (e.g., dhBBR) is administrated to humans through the same route (p.o.) and form (powder mixed with food) used in animal studies. EX1003, ¶68.

Claim 7	Claim 7 is rendered obvious by Turner in view of Shaw
The method of claim 1 wherein the dihydroberberine is administered at least once daily.	Turner teaches that the dihydroberberine is administered at least once daily on rodents. EX1003, ¶69. • "Mice and rats were fed for 10 weeks and 4 weeks, respectively, and based on pilot testing for dhBBR in mice, BBR and dhBBR were provided in the HFD at

	a dose of 100 mg · kg^{-1} · **day**$^{-1}$ for the **final 2 weeks of feeding**." EX1004 at 1415 (emphasis added). A POSA would have been motivated to administer dhBBR to humans at least once daily. EX1003, ¶¶69-70. A POSA would have a reasonable expectation of success when the POSA tries to administer dhBBR daily to humans for managing glucose tolerance. *Id*.

V. GROUND 2: CLAIM 5 IS RENDERED OBVIOUS BY TURNER IN VIEW OF SHAW AND FURTHER IN VIEW OF ZHANG.

As shown in Section IV.A above, Claim 1 is rendered obvious by Turner in view of Shaw. Claim 5 depends from Claim 1 and introduces the added limitation of orally administering dhBBR to an individual as a capsule or tablet. Because Turner teaches that dhBBR is dry and solid, and Zhang teaches that BBR has already been administrated orally in tablet form, a POSA would find it obvious to try to administrate dhBBR (a derivative of BBR) as a substitute oral drug also in tablet form. As explained in further detail, Claim 5 is rendered obvious by Turner in View of Shaw and further in view of Zhang.

Claim 5	Claim 5 is rendered obvious by Turner in view of Shaw and further in view of Zhang.

The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Turner teaches that dihydroberberine can be synthesized and kept in a dry and solid form. EX1003 at ¶72. • EX1004¸ Supplementary Methods, Preparation of Dihydroberberine ("the filter cake was dried overnight to give dihydroberberine sulfate [5,6-Dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium sulfate] (2.9 g, yield 75%)." Turner teaches that BBR is administered orally. EX1003 at ¶71. EX1004 at 1414 ("BBR is commonly used as a nonprescription oral drug in China to treat gut infections and diarrhea with few side effects, and its therapeutic potential for the treatment of diabetes … in humans has been reported.") Turner further teaches the dihydroberberine is administered orally because it discloses that dhBBR is administered to the mice the same way BBR is administered in the HFD diet. EX1003 at ¶72. • "Mice and rats were fed for 10 weeks and 4 weeks, respectively, and based on pilot testing for dhBBR in

	mice, BBR and dhBBR were provided in the HFD at a dose of 100 mg · kg^{-1} · day^{-1} for the final 2 weeks of feeding." EX1004 at 1415. Zhang teaches that BBR has been administrated orally in tablet form. EX1003 at ¶73. EX1006 at 2560 (conducting a clinical study on the efficacy and safety of BBR for treating diabetes where patients "were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets.") Because Turner teaches that dhBBR is dry and solid and being administrated orally, and because Zhang teaches that BBR has already been administrated orally in tablet (a dry and solid) form, a POSA would find it obvious to try to administrate dhBBR (a derivative of BBR) as a substitute oral drug also in tablet form. EX1003, ¶¶71-73. Administering dhBBR as a tablet would also be obvious to a POSA because it is one of the few well known and common forms for administering solid medications orally. EX1003, ¶64.

VI. GROUND 3: CLAIMS 1, 2, 5 AND 7 ARE RENDERED OBVIOUS BY ZHANG IN VIEW OF FENG

A. Claim 1 Is Obvious

1. Zhang Discloses Clinical Studies Demonstrating that BBR is effective in managing glucose tolerance of humans.

Zhang reported "a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of diabetes and dyslipidemia." EX1006 at 2560. The Zhang clinical trials involved screening and selecting many type 2 diabetes patients across four hospital centers. *Id*. These patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets. *Id*. The studies were conducted for up to three months. *Id*. at 2561. The patients' fasting glucose levels were measured and recorded at months 0, 1, 2, and 3. *Id*. at 2561, Fig. 3(B). The results of the study showed that patients "receiving berberine had a significant improvement in fasting plasma glucose" "[a]s compared with subjects who received placebo." *Id*. at 2561. The studies also found that "[n]o serious adverse events occurred. Mild to moderate constipation occurred in five participants receiving berberine and one participant in the placebo group. However, the frequency of constipation was not significantly different between the berberine and placebo groups (P = 0.207)." *Id*. at 2563. In conclusion, Zhang stated that berberine is effective and safe in the treatment of type 2 diabetes. *Id*. at 2559. *See also* EX1003, ¶82.

2. A POSA is motivated to find a more bioavailable derivative of BBR for diabetes treatment.

BBR is widely known to "exhibit[] poor water solubility." EX1007 (Feng) at 2. It is also well documented that BBR is presumed to be "very difficult for intestinal epithelial to absorb." *Id*; *see also* EX1004 (Turner) at 1417 ("A potential disadvantage of BBR as an in vivo compound for treatment of diabetes is that we and others have previously reported the need for relatively high doses in rodents to achieve beneficial metabolic effects.") As such, a POSA would be motivated to find a more bioavailable derivative of BBR. EX1003, ¶83.

3. dhBBR is a known BBR derivative with improved absorption characteristics.

There are multiple reports in the literature predicting and demonstrating that dhBBR, as a BBR derivative, has improved absorption characteristics. dhBBR was predicted to have improved absorption characteristics based on a structural analysis of the molecules where BBR is found to possess "an extremely flat configuration, which is likely to have limited absorption across the intestinal epithelia" but "derivatization to dhBBR was predicted to open up the structure, making it more amenable to uptake." EX1004 (Turner) at 1417. *See also* EX1003, ¶84.

More importantly, the prediction of dhBBR's improved absorption characteristics was confirmed by preclinical studies. Such studies include pharmacokinetic analyses of rodent models. Turner's studies showed that following

oral administration (by gavage, not in high fat diet) of 20 mg/kg BBR, BBR was not detected in the plasma. In contrast, dhBBR at the same dose was rapidly detected in the plasma with a C_{max} of approximately 2.8 ng/ml and half-life of 3.5 hrs. EX1004 at 1416, Supp. Fig. 2. Interestingly, the half-life and Cmax value for BBR detected in the blood were both significantly larger than that for the dhBBR detected in the blood. *Id*. at 1416, Supp. Fig. 2(C). The authors concluded that dhBBR gets "rapidly converted back to BBR" soon once it was absorbed based on its pharmacokinetic analyses. *Id.* at 1417. *See also* EX1003, ¶85.

The preclinical studies also include *in vivo* and *in vitro* studies of the metabolism of BBR in gut microbiota. Here, Feng teaches that dhBBR was identified as a metabolite in the intestines of rodents fed on a BBR diet. EX1007 (Feng) at Fig. 1(C). Feng performed additional *in vitro* studies where BBR was incubated with bacteria isolated from rodent intestines as well as bacteria isolated from human intestines. *See id.* at 2-3, Fig. 1(d). The results confirmed that the bacterial from the guts converted BBR to dhBBR. *Id*. Feng then performed *in vitro* studies using the Caco-2 cell line (a widely used human intestinal epithelial cell model) to examine how dhBBR compares with BBR in terms of the rate of absorption by the intestines. *Id*. at 5 & Fig. 3(a). Feng also administered dhBBR and/or BBR to rats and performed *in vivo* concentration-time curve studies to further examine how dhBBR compares with BBR in terms of the rate of absorption by the intestines. *Id*. at Fig.

3(b)-3(d). Both the *in vivo* and *in vitro* studies confirm that dhBBR has an intestinal absorption rate higher than that of BBR. Interestingly, the authors found that dhBBR gets reverted to BBR via oxidization soon after dhBBR enters the intestine tissues. *Id.* at 6-7. Based on their findings, Feng concluded that "the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." *Id.* at 1. *See also* EX1003, ¶86.

4. It would be obvious for a POSA to try dhBBR as an alternative to BBR for managing blood glucose levels.

Because both Feng and Turner teach that dhBBR has improved absorption characteristics, it would have been obvious for a POSA to try dhBBR as an alternative to BBR to reduce dosage. EX1003, ¶87. Also, because both Feng and Turner teach that dhBBR gets rapidly converted back to BBR after absorption in intestine tissues and enters the blood, a POSA would understand that an orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro-drug. EX1003, ¶87. A patentee may not overcome an obviousness challenge if "the inventors merely used routine research methods to prove what was already believed to be the case." *Pharmastem Therapeutics, Inc. v. Viacell, Inc.*, 491 F.3d 1342, 1363 (Fed. Cir. 2007).

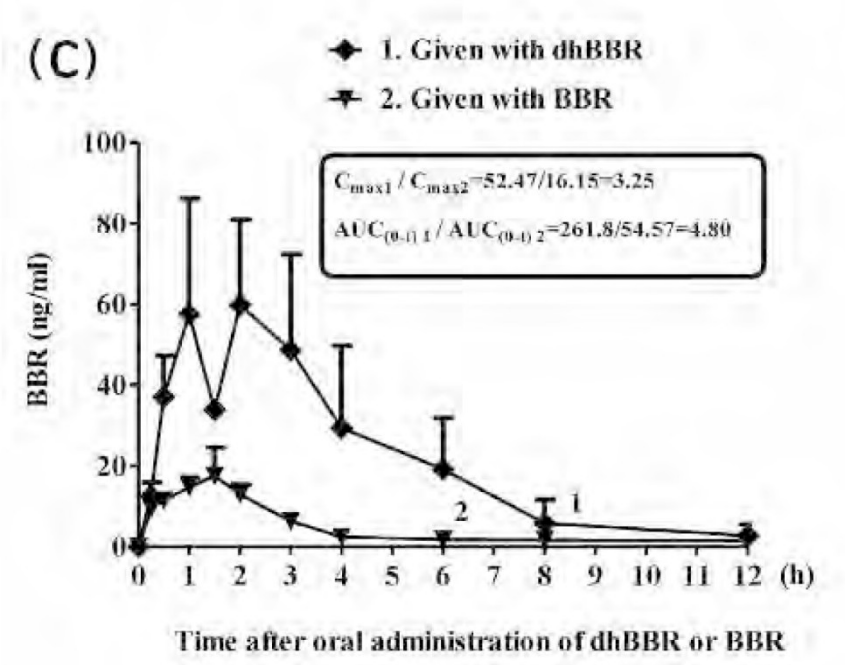
Moreover, because BBR is converted to dhBBR by the gut microbiota after the oral administration of BBR, dhBBR had been effectively administered to human

for decades as BBR. Thus, dhBBR would be safe to be administered to humans at the appropriate dosage amount as for the berberine drug. *See also* EX1003, ¶87.

5. A POSA will have a reasonable expectation of success that dhBBR can be administered at a pharmaceutically effective dosage that is at least five-fold lower than BBR's dosage.

Feng concluded that "dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption." EX1007 at 8. As such, a POSA would have been motivated to use dhBBR, which readily transforms to berberine after absorption, as a low dosage substitute of berberine for oral administration for the treatment of diabetes and managing glucose tolerance in humans.

The reasonable expectation of success is corroborated by the experimental results taught in Feng. EX1003, ¶89. Feng demonstrated through *in vivo* animal studies that an orally administered dhBBR would have a higher intestinal absorption and a much higher level of BBR would be detected in the blood over an extended period. Specifically, the blood level of BBR in the dhBBR-treated rats exhibited C_{max} value that was 3.25-fold higher than those of the BBR-treated rats. EX1007 at 5. The result was documented in Fig. 3(c), which is reproduced below. *Id*. A 3.25-fold reduction of the 1,000 mg/day BBR dosage taught by Zhang would reduce the dhBBR dosage to approximately 300 mg/day, which is within the claimed 25 mg to 800 mg dosage range. *See In re Peterson*, 315 at 1329; EX1003, ¶ 89.



Feng also taught the $P_{app(AP\text{-}BL)}$ (apparent permeability coefficient of apical-basolateral) coefficient for dhBBR was 11.9-fold higher than that for BBR based on *in vitro* human Caco-2 cell model studies. EX1007 at 5. Regardless of whether the $P_{app(AP\text{-}BL)}$ coefficient accurately reflects how a human's dhBBR intestinal absorption rate compares with the BBR absorption rate, a 12-fold reduction of the BBR dosage amount taught in Zhang would reduce the dhBBR dosage to approximately 83.3 mg/day, which still places the pharmaceutically effective dhBBR dosage within the claimed 25 mg to 800 mg dosage range. *See In re Peterson*, 315 at 1329.

6. Invalidity Claim Chart for Claim 1

Provided below is an invalidity claim chart for Claim 1 summarizing the above analysis.

Claim 1	Claim 1 is Rendered Obvious by Zhang in View of Feng
A method of managing glucose tolerance in an individual, the method comprising:	To the extent the preamble is limiting, Zhang teaches a method of managing glucose tolerance in humans because Zhang discloses treatment of diabetic patients. EX1003, ¶74. • "in the present study, we performed a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the treatment of diabetes and dyslipidemia." EX1006 at 2560. • "As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose and …" EX1006 at 2561.
administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the	Zhang teaches a method of managing glucose tolerance in humans. EX1003, ¶75. • "in the present study, we performed a randomized, double-blind, placebo-controlled trial in four centers to evaluate the efficacy and safety of berberine in the

pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.	treatment of diabetes and dyslipidemia." EX1006 at 2560. • "As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose and …" EX1006 at 2561. Zhang discloses that the administration of BBR at a dosage of 1g (1,000 mg) / day to type 2 diabetic patients would be pharmaceutically effective for treating diabetes. EX1003, ¶¶76-77. • "Eligibility criteria were: 1) age of 25–70 yr; 2) newly diagnosed type 2 diabetes according to the 1999 World Health Organization criteria …" EX1006 at 2560. • "Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets." EX1006 at 2560. 0.5g x 2 (twice daily) equals 1g (1,000mg)/day.

	• "As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose and …" EX1006 at 2561. Zhang in view of Feng teaches that administering dhBBR to humans at a dosage that is reduced from the pharmaceutically effective BBR dose of 1g/day would fall within the claimed "approximately 25 mg to approximately 800 mg" dosage range. EX1003, ¶¶78-81. • "Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets." EX1006 at 2560. 0.5g x 2 (twice daily) equals 1g (1,000mg)/day. • "As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose …" EX1006 at 2561.

	• "Here, we show that the gut microbiota converts BBR into its absorbable form of dihydroberberine (dhBBR), which has an intestinal absorption rate 5-fold that of BBR in animals." EX1007 at Abstract. • dhBBR "has an intestinal absorption rate 5-fold that of BBR in animals." EX1007 at 1. • "First, the absorption of BBR and dhBBR was investigated in the Caco-2 cell model. In this *in vitro* system, dhBBR displayed significantly improved absorption as compared with BBR. The $P_{app\ (AP\text{-}BL)}$ (apparent permeability coefficient of AP-BL; AP: apical; BL: basolateral) for dhBBR was 11.9-fold higher than that for BBR (4.51×10^{-6} cm/s vs. 0.38×10^{-6} cm/s), suggesting that the bioavailability of dhBBR for absorption was markedly increased (Fig. 3a, L)." EX1007 at 5. • 1,000 mg/day divided by 5 is 200 mg/day. • 1,000 mg/day divided by 12 is 83.3 mg/day.

	A POSA will have a reasonable expectation of success that dhBBR can be administered at a pharmaceutically effective dosage that is at least five folds lower than BBR's dosage. *See supra* at VI.A.1-5. Zhang in view of Feng further teaches that administering dhBBR would be pharmaceutically effective to manage human's blood glucose levels because dhBBR is a transient form of BBR and that dhBBR gets rapidly converted back to BBR after absorption in intestine tissues and enters the blood. In other words, an orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro-drug. EX1003, ¶80. • "dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption." EX1007 at 8. • "Conclusively, the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." EX1007 at 1.

	Feng's findings are further corroborated by Turner. EX1003, ¶80. • "Our pharmokinetics data were consistent with this prediction, with dhBBR displaying improved absorption compared with BBR. Intriguingly, our data also revealed that once absorbed, dhBBR was rapidly converted back to BBR, highlighting the fact that this is likely the active moiety." EX1004 at 1417. A POSA would be motivated to modify Zhang's teachings and substitute BBR with dhBBR for managing glucose tolerance with reasonable expectation of success, for the following reasons. • A POSA is motivated to find a more bioavailable derivative of BBR for diabetes treatment. EX1003 at ¶83. *See supra* at VI.A.1-2. • dhBBR is a known BBR derivative with improved absorption characteristics. EX1003 at ¶¶84-86. *See supra* at VI.A.3.

	• A POSA will have a reasonable expectation of success that dhBBR, as an alternative to BBR for managing blood glucose levels, can be administered at a pharmaceutically effective dosage that is at least five-fold lower than BBR's dosage. EX1003 at ¶¶87-90. *See supra* at VI.A.4-5.

B. Claims 2, 5 and 7 Are Obvious

Claim 2	Claim 2 is Rendered Obvious by Zhang in View of Feng
The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels.[14]	Zhang teaches that administration of BBR reduces fasting glucose levels. EX1003, ¶91. • "As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose …" EX1006 at 2561, Fig. 3(B). Zhang in view of Feng further teaches that administering dhBBR would be able to reduce fasting glucose levels because dhBBR is a transient form of BBR and that dhBBR gets rapidly converted back to BBR after

[14] *See supra* fn. 13.

	absorption in intestine tissues and enters the blood. In other words, an orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro-drug. EX1003, ¶¶92-93. • "dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption." EX1007 at 8. • "Conclusively, the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." EX1007 at 1. Feng's findings are further corroborated by Turner. EX1003, ¶93. • "Our pharmokinetics data were consistent with this prediction, with dhBBR displaying improved absorption compared with BBR. Intriguingly, our data also revealed that once absorbed, dhBBR was rapidly converted back to BBR, highlighting the fact that this is likely the active moiety." EX1004 at 1417.

	For reasons stated in *supra* at VI.A.1-5, a POSA would have been motivated to modify Zhang with Feng with a reasonable expectation of success. *See also* EX1003, ¶¶93-94.

Claim 5	Claim 5 is Rendered Obvious by Zhang in View of Feng
The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Zhang teaches that the BBR is administered as tablets. EX1003, ¶95. • "Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets." EX1006 at 2560. Feng teaches that berberine "ha[d] been used orally for decades in China as an over-the-counter (OTC) drug to treat diarrhea with good safety." EX1007 at 2. Feng teaches that dhBBR can be and was indeed administered orally to rodent models to study its rate of absorption by the intestines. EX1003, ¶96; EX1007 at 5, 12 ("Five SD rats were fasted for 12h and then orally administered 200mg/kg dhBBR. … BBR served as a control in the study"). Feng further discloses that

	"dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption." EX1007 at 8. Feng further discloses that "the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." EX1007 at 1. This finding is corroborated by Turner. EX1003, ¶97. • "Our pharmokinetics data were consistent with this prediction, with dhBBR displaying improved absorption compared with BBR. Intriguingly, our data also revealed that once absorbed, dhBBR was rapidly converted back to BBR, highlighting the fact that this is likely the active moiety." EX1004 at 1417. A POSA therefore would understand an orally administered dhBBR would remain pharmacologically effective because BBR would enter the blood and remain as the active drug and dhBBR acts as a pro-drug. EX1003, ¶97.

	Because it is well known that BBR is to be administered orally in tablets to patients, and further because an orally administered dhBBR would remain pharmacologically effective because BBR would remain as the active drug and dhBBR acts as a pro-drug, a POSA would have been motivated to administer dhBBR orally in tablets to improve intestinal absorption rate. EX1003, ¶98. For reasons stated in *supra* at VI.A.1-5, a POSA would have been motivated to modify Zhang with Feng with a reasonable expectation of success. *See also* EX1003, ¶98

Claim 7	Claim 7 is Rendered Obvious by Zhang in View of Feng
The method of claim 1 wherein the dihydroberberine is administered at least once daily.	Zhang teaches that BBR is administered at least once daily. EX1003, ¶99. • "Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets." EX1006 at 2560. Feng concludes that "dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical

	characteristics for absorption." EX1007 at 8. Feng further discloses that dhBBR "has an intestinal absorption rate 5-fold that of BBR in animals." *Id*. at 1; Abstract. *See also* EX1003, ¶100. Feng further discloses that "the gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine tissues and enters the blood." EX1007 at 1; EX1003, ¶101. This finding is corroborated by Turner. EX1003, ¶101. • "Our pharmokinetics data were consistent with this prediction, with dhBBR displaying improved absorption compared with BBR. Intriguingly, our data also revealed that once absorbed, dhBBR was rapidly converted back to BBR, highlighting the fact that this is likely the active moiety." EX1004 at 1417. Because BBR has already been administered orally at least once daily, and further because orally administered dhBBR would remain pharmacologically effective given BBR would enter the blood and remain as the

	active drug and dhBBR acts as a pro-drug, a POSA would have been motivated to administrate dhBBR similarly - at least once daily. EX1003, ¶102. For reasons stated in *supra* at VI.A.1-5, a POSA would have been motivated to modify Zhang with Feng with a reasonable expectation of success. EX1003, ¶102.

VII. GROUND 4: CLAIM 6 IS RENDERED OBVIOUS BY ZHANG IN VIEW OF FENG AND FURTHER IN VIEW OF TURNER.

As shown in Section VI.A above, Claim 1 is rendered obvious by Zhang in view of Feng. Claim 6 depends from Claim 1 and introduces the added limitation of orally administering dhBBR as either a "food product" or a "beverage product." Because Turner teaches administering dhBBR to rodents as food product for managing glucose tolerance, a POSA would find it obvious to try administering dhBBR as a food product to humans to manage glucose tolerance. As explained in further detail, Claim 6 is rendered obvious by Zhang in view of Feng and further in view of Turner.

Claim 6	Claim 6 is rendered obvious by Zhang in view of Feng and further in view of Turner.
The method of claim 1 wherein the	Turner teaches that the dihydroberberine is administered orally as part of the diet food because it

dihydroberberine is orally administered as at least one of a food product or beverage product.	discloses that dhBBR is administered to the mice the same way BBR is administered in a HFD diet. EX1003, ¶104. • "Mice and rats were fed for 10 weeks and 4 weeks, respectively, and based on pilot testing for dhBBR in mice, BBR and dhBBR were provided in the HFD at a dose of 100 mg · kg^{-1} · day^{-1} for the final 2 weeks of feeding." EX1004 at 1415. Turner teaches that dihydroberberine can be synthesized and kept in a dry and solid form. EX1003, ¶103. • EX1004, Supplementary Methods, Preparation of Dihydroberberine ("the filter cake was dried overnight to give dihydroberberine sulfate [5,6-Dihydro-9,10-dimethoxybenzo(g)-1,3-benzodioxolo(5,6-a) quinolizinium sulfate] (2.9 g, yield 75%)." A POSA would have been motivated to administer dhBBR orally to humans "as at least one of a food product" because a POSA would have a reasonable

	expectation of success where the same medicine (e.g., dhBBR) is administered to humans through the same route (p.o.) and form (powder mixed with food) used in the animal studies such as the Turner studies. EX1003, ¶106. Finally, a POSA would have been motivated to combine the teachings of Turner with Zhang and Feng because Feng specifically referenced Turner as supporting Feng's findings. EX1007 at 5 ("DhBBR in its sulfate form (dihydroberberine sulfate) was previously reported to exhibit better absorption in the intestine as compared with BBR."); EX1003, ¶105.

VIII. COMPLIANCE WITH FORMAL REQUIREMENTS

A. Mandatory Notices Under 37 C.F.R. §§ 42.8(b)(1)-(4)

1. Real Party-In-Interest

Petitioner certifies that Bonerge Lifescience (Hunan) Co., Ltd is the real party-in-interest.

2. Related Matters

Petitioner identifies the following related matter:

Nanjing Nutrabuilding Bio-Tech Co., Ltd. v. Bonerge Lifescience (Hunan) Co., Ltd. et al., No. 5:25-cv-00271-JGB-SHK (C.D. Cal.).

3. Lead and Backup Counsel

Petitioner provides the following counsel information. Pursuant to 37 C.F.R. § 42.10(b), a Power of Attorney accompanies this Petition.

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4. Service Information

Petitioner consents to service by email on the following email addresses: john.handy@rimonlaw.com; jason.xu@rimonlaw.com; HuaChen@ScienBiziPPC.com.

B. Standing

In accordance with 37 C.F.R. § 42.104(a), Petitioner certifies that the ’961 patent is available for *inter partes* review and that Petitioner is not barred or estopped from requesting an *inter partes* review challenging the Challenged Claims on the grounds identified in this Petition.

C. Fees

The Office is hereby authorized to charge the fee set forth in 37 C.F.R. § 42.15(a) and any additional fees that might be due in connection with this Petition to Deposit Account No. 50-5992.

IX. CONCLUSION

For the foregoing reasons, Petitioner requests that the Board institute trial and cancel the Challenged Claims of the ’961 patent.

DATE: September 26, 2025

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 word count for this Petition totals 12,005 words, excluding the parts of the brief exempted by 37 C.F.R. § 42.24(a), as calculated by Microsoft Word, which is less than the 14,000 allowed under 37 C.F.R. § 42.24(a)(i).

DATE: September 26, 2025

Respectfully submitted,

/s/ *John Handy*

John Handy
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 Petition for *Inter Partes* Review of U.S. Patent No. 10,278,961, including its supporting Exhibits and Powers of Attorney has been served on September 26, 2025 upon the following litigation counsel via electronic means:

- Mark Nielsen (mark.nielsen@solidcounsel.com)
- Wook Pak (wook@cislo.com)

DATE: September 26, 2025

Respectfully submitted,

/s/ *John Handy*

John Handy
Registration No. 68,906
Counsel for Petitioner

APPENDIX A: CHALLENGED CLAIMS

Claim	Claim Language
1	A method of managing glucose tolerance in an individual, the method comprising: administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.
2	The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels.
5	The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.
6	The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.
7	The method of claim 1 wherein the dihydroberberine is administered at least once daily.

Assignment Center

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Patent assignment abstract of title

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Invention titleADMINISTRATION OF BERBERINE METABOLITES

InventorsRyan Lowery, Jacob Wilson, Shawn Wells, Terry LaCore

Patent number10278961

Issue date May 7, 2019

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International number N/A

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