

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.

IPR2025-01593
Patent 10,278,961

Before KAREN I. SWEENEY, *Trial Paralegal*

DECLARATION OF DR. LOUIS J. DEFILIPPI, PH.D.

SUBMITTED IN REBUTTAL TO THE DECLARATION OF DR. RONALD

J. SHEBUSKI, SR., PH.D.

Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd., hereby respectfully submits the following Declaration of Dr. Louis J. DeFilippi, Ph.D. to the Board in support of Patent Owner's Response to the Petition.

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TABLE OF EXHIBITS

EXHIBIT NUMBER	DESCRIPTION
2154	Sofianos Andrikopoulos, Amy R. Blair, Nadia Deluca, Barbara C. Fam and Joseph Proietto (2008) Evaluating the Glucose Tolerance Test in Mice, Am. J. Physiol. Endocrinol Metab. 295(6), E1323-1332 doi:10.1152/ajpendo.90617.2008
2155	ATCC, L6 cell information (https://www.atcc.org/products/crl-1458) (accessed July 2026)
2156	Bracken, M.B. (2008) Why animal studies are often poor predictors of human reactions to exposure, J. R. Soc. Med. 101:120-122. DOI 10.1258/jrsm.2008.08k033
2157	Blanchard, O.L. and Smoliga, J.M., (2015) Translating dosages from animal models to human clinical trials—revisiting body surface area scaling, FASEB J. 29(5), 1629-1634 https://doi.org/10.1096/fj.14-269043
2158	Nathan D.M. et al. (2007) Impaired Fasting Glucose and Impaired Glucose Tolerance, Diabetes Care 30(3), 753-759
2159	S.S. Rao, P. Disraeli, T. McGregor (2004) Impaired Glucose Tolerance and Impaired Fasting Glucose, Am. Family Physician 69(8), 1961-1968
2160	Frazier, D.L. and Price, G.S. (1998) Use of Body Surface Area to Calculate Chemotherapeutic Drug Dose in Dogs: II. Limitations Imposed by Pharmacokinetic Factors, J. Vet. Int. Med. 12(4), 272-278
2161	A. Mark Clarfield (2009) Book Review of The Discovery Of Insulin: Twenty-Fifth Anniversary Edition by Michael Bliss, JAMA, 301(15), 1607-1608
2162	Robinson, P.K. (2015) Enzymes: principles and biotechnological applications, Essays Biochem. (2015) 59, 1-41 doi: 10.1042/BSE0590001
2163	Excerpt from T. Palmer and P.L. Bonner (2007) ENZYMES: Biochemistry, Biotechnology and Clinical Chemistry, Second Edition, text page 74
2164	Curriculum Vitae of Dr. Louis J. DeFilippi

DECLARATION OF DR. LOUIS J. DEFILIPPI, PH.D.

I, Louis J. DeFilippi, Ph.D. declare as follows:

I. INTRODUCTION

A. Background of Dr. Louis DeFilippi

1. I have been engaged to submit a rebuttal to the Declaration of Ronald J. Shebuski, Sr., Ph.D., which I understand was submitted in support of Petitioner Bonerge Lifescience (Hunan) Co., Ltd.'s ("Petitioner" or "Bonerger") Petition for Inter Partes Review.

2. The following section contains a summary of my educational background, career history, patents and/or publications, and other relevant qualifications. My full curriculum vitae is attached as Exhibit 2164 submitted with this declaration.

3. I hold a Ph.D. in biological chemistry, conferred by the Department of Biological Chemistry, The University of Michigan Medical School, and work as a consulting biochemist. I have worked in such diverse areas as the discovery of novel proteins in the blood, blood storage, using enzymes to make sweeteners, to enzymatically convert natural products to useful applied biotechnology and novel ingredient formulations (discovered that these compounds provide a springboard into a broad spectrum of formulating applications within the personal care and over-the-counter (OTC) product categories with multi-functional properties, and as a result provide a multitude of unexpected benefits and superior characteristics to skin,

hair, bath, dental and OTC products) pharmaceuticals, application of antimicrobials, biological treatment of hazardous waste, microorganisms to recycle urine and wastewater on the Space Station and Mars Lander, as well as aiding customers in complying with OSHA, EPA, FDA and USDA regulations, mostly in the food industry. I have developed the commercial scale-up for the critical enzymatic step to produce the first once-a-day AIDS treatment emtricitabine (formerly known as Coviracil). I have served as an expert witness in these fields and others in a variety of legal proceedings. I have been active as a Director in the Chicago Section American Chemical Society. A copy of my complete CV, which describes my educational background and qualifications, is included in Exhibit 2164, submitted herewith.

4. As a teaching assistant at The University of Michigan I performed research on the purification and characterization of unique blood proteins. Much of this work involved spectrophotometry of binding and redox (reduction / oxidation) reactions, as well as related prosthetic groups, including the heme *a* from cytochrome c oxidase (aka respiration complex IV). Also, while at The University of Michigan, I taught introductory biochemistry in the undergraduate laboratory (to students which included many pre-med students), and also taught chemistry, biochemistry and applied physiology to BS Nursing students and Medical Technologists. My teaching to the Medical Technologists included full hands-on training on performing clinical

glucose tolerance tests, blood drawing, glucose analysis and relevant data work-up. When I was at Cornell University, I was a Postdoctoral Scholar, performed research on blood proteins, and taught introductory biochemistry. As an adjunct professor at Columbia College, I taught the general Chemistry / Biochemistry course. In each of these courses I presented lectures on enzymatic processes, including small molecule transformation processes.

5. I am a named inventor on 15 patents directed in the biotechnology, chemical, food, pharmaceutical, and biological air and wastewater treatment arts. Within that group, I am a named inventor on multiple patents involving immobilized enzymes and immobilized enzyme-catalyzed processes, including a number involving enzymatic transformations, such as:

6. Laszlo, Joseph A., Compton, David L., DeFilippi, Louis J. and Grall, Steven, "Methods of Making Composition Comprising a UV-Absorbing Chromophore", U.S. Patent 7,572,610 (2009).

7. Laszlo, Joseph A., Compton, David L., DeFilippi, Louis. J. and Grall, Steven, "Compositions Comprising a UV-Absorbing Chromophore", U.S. Patent 7,727,514 (2010).

8. DeFilippi, Louis J., Grall, Steven G., Kinney, James F., Laszlo, Joseph A., Compton, David L.; "Formulations with Feruloyl Glycerides and Methods of Preparation", U.S. Patent 7,744,856 (2010).

9. Laszlo, Joseph. A., Compton, David. L., DeFilippi, Louis J. and Grall, Steven, “Compositions Comprising a UV-Absorbing Chromophore”, U.S. Patent 8,357,353 (2013).

10. I have been retained as a technical expert on multiple litigation matters. Most recently (~five years) I have testified as an expert at trial and/or by deposition in the following matters:

11. In the Matter of Certain Plant-Derived Recombinant Human Serum Albumins (“rHSA”) and Products Containing Same, USITC Inv. No. 337-TA-1238 (retained by respondent Wuhan Healthgen Biotechnology Corp., deposed May and July 2021, testified November 2021).

12. Celanese Int’l Corp. v. Anhui Jinhe Industrial Co., Case 1:20-cv-01775-UNA and In the Matter of Certain High-Potency Sweeteners, Processes for Making Same, and Products Containing Same, USITC Inv. No. 337-TA-1264 (retained by Celanese, deposed December 2021).

13. Longhorn Vaccines & Diagnostics, LLC v. Spectrum Solutions, IPR Nos. IPR2021-00847, IPR2021-00850, IPR2021-00854, IPR2021-00857, IPR2021-00860 (retained by Longhorn Vaccines & Diagnostics, deposed April and August 2022).

14. Silcotek Corp. v. Waters Corp., C.A. No. 23-281-JPM (retained by Waters Corp., deposed January 2024).

15. Pogona, LLC, Plaintiff, v. MERCK SHARP & DOHME LLC, Defendant, U.S. District Court, NJ (retained by Pogona, February 2026; deposition date not yet set).

16. The above cases have included such subject areas as chemically or biochemically altered natural products, such as the transesterification of ferulic acid with soybean oil, transesterification of jojoba oil with hydrogenated jojoba oil (addition of hydrogen to natural molecule) as well as biologically altered natural and synthetic products.

17. Purposely left blank.

II. COMPENSATION

18. For my efforts in connection with the preparation of this declaration, I am being compensated at an hourly rate of \$825.00. My compensation is not in any way contingent on my performance, the result of this proceeding, or any of the issues involved therein. I am also being reimbursed for expenses incurred as a result of activities performed as an expert.

19. If called to testify as to the contents of this report, I can and would testify truthfully and competently.

III. MATERIALS REVIEWED

20. In preparing this declaration, I have reviewed and/or considered the Declaration of Ronald J. Shebuski, Sr., Ph.D., the Petition for Inter Partes Review

Paper 2), the documents cited in the List of Patent Owner's Exhibits cited herein, the documents listed in Dr. Shebuski's declaration, as well as the documents referenced in this declaration. In forming my opinions, I have considered the materials cited and referenced herein. I have also relied on my own understanding and expertise of the subject matter.

IV. RELEVANT LEGAL STANDARDS

21. I am not a lawyer. I have been provided with an understanding of the legal principles that govern patent validity and claim construction. I have conducted my analysis in conformance with these principles. I set forth those understandings below.

A. Obviousness

22. Patent Owner's counsel has informed me that the issue to contend with in this matter is obviousness, which is governed by Title 35 United States Code ("U.S.C.") § 103. The statute provides that a "patent may not be obtained ... if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which the subject matter pertains." I have also been informed that issued patents are presumed to be valid. 35 U.S.C § 282(a).

23. The patent owner's counsel informed me that in an inter partes review, the

Petitioner has the burden of proving, by a preponderance of the evidence, that the challenged patent claims would have been obvious based on “prior art” before the effective filing date of the claimed invention (i.e., before April 19, 2016).

24. For purposes of this report, I understand that “prior art” consists of patents, patent applications, and printed publications that existed prior to April 19, 2016, if not prior to April 19, 2015.

25. I have been informed that when a single prior art reference does not contain every limitation or element of a single patent claim, the PTAB can only invalidate the claim if supplying the missing limitations through another prior art reference or modification of the existing prior art would have been obvious to a person of ordinary skill in the art, and doing so without applying hindsight bias (i.e., looking back to prior to April 19, 2016 based on what is currently known so as to recreate the current invention in the prior art through what is now known because of the invention). I have been further informed that a claim is invalid for obviousness only if the differences between the claimed invention and the prior art are such that the claimed invention, as a whole, would have been obvious to a person having ordinary skill in the art before the effective filing date of the claimed invention, again without the benefit of hindsight.

26. As part of the obviousness analysis, I have been informed that prior art references may be combined to show that a patent claim is invalid as obvious. I also

understand that an obviousness evaluation may be based on a single reference or a combination of prior art references. For example, a single reference—when considered in light of the knowledge of a person of ordinary skill in the art—may render a claim obvious. Where a Petitioner attempts to prove obviousness by merely throwing metaphorical darts at a board in hopes of arriving at a successful result where the prior art gave either no indication of which parameters were critical or no direction as to which of many possible choices is likely to be successful, hindsight claims of obviousness may be rejected.

1. *Graham* Factors

27. Counsel for the Patent Owner has informed me that an obviousness analysis considers a number of factors that consider four factual inquiries underlying obviousness, otherwise known as the *Graham* factors. I have been informed that the inquiries are as follows: (1) the scope and content of the prior art; (2) the differences between the claimed invention and the prior art; (3) the level of ordinary skill in the art; and, (4) objective evidence of non-obviousness (otherwise known as the secondary considerations of non-obviousness).

a. Scope and Content of the Prior Art

28. I have been informed that for a reference to be proper for use in an obviousness rejection, it must be dated prior to April 19, 2016. I also understand that the prior art should be considered for all that it teaches, and not just be “cherry

picked.” I have further been informed that in order to be proper for use in an obviousness challenge, the reference must be “analogous” art to the claimed invention in the patent. Prior art is considered non-analogous unless it is (1) from the same field of endeavor as the claimed invention, or (2) reasonably pertinent to the particular problem faced by the inventor.

b. Differences Between the Claimed Invention and the Prior Art

29. I have been informed that an obviousness analysis requires that the differences between what is claimed in the patent under consideration and the prior art be ascertained.

c. Level of Ordinary Skill in the Art

30. The Patent Owner’s counsel has informed me that my analysis must be performed from the perspective of a hypothetical “person of ordinary skill in the art” (“POSITA”) as of the effective filing date of the patent, which I understand to be April 19, 2016. I understand that a POSITA is a hypothetical person who is presumed to be aware of all pertinent prior art, has ordinary skill in the field of the invention, and is a person of ordinary creativity. I understand that my analysis should not be performed using a present-day perspective, and that I should not use hindsight.

d. Secondary Considerations of Non-Obviousness

31. Patent owner’s counsel informed me that evidence of nonobviousness—

sometimes called “secondary considerations” or “objective indicia”—must be considered when present. These factors include commercial success, long-felt but unmet need, failure of others, industry praise, unexpected results, copying, licensing or licensing interest, and skepticism of experts.

32. I have been informed that when a prior art reference suggests that the line of development flowing from the reference’s disclosure is unlikely to be productive of the result sought by the applicant the prior art referenced may be said to “teach away” from the claimed invention.

2. Motivation to Combine with a Reasonable Likelihood of Success

33. I have been informed that after considering the scope and content of the prior art and identifying the differences between the prior art and the challenged claims, if any, the obviousness inquiry evaluates whether a person of ordinary skill in the art would have been motivated to combine or modify the existing prior art to bridge the differences between the prior art and the claimed invention; and if so, whether a person of ordinary skill in the art would have had a reasonable expectation of likelihood of success in doing so.

a. Motivation to Combine

34. Assuming a challenger demonstrates that all of the elements of the invention are present in the prior art combination and/or modification proposed, the

challenger must then also demonstrate that there would be a reason to combine or modify the prior art references to arrive at the claimed invention. I am informed that the question is whether a POSITA would have combined elements from specific references in the way the claimed invention does (i.e., to arrive at the claims' actual limitations). I am further informed that a patent composed of several elements is not proved obvious merely by demonstrating that each of its elements was, independently, known in the prior art. Finally, I have further been informed that a motivation to combine must be based on articulated reasoning with some rational underpinning.

b. Reasonable likelihood of Success

35. A reasonable likelihood of success in the combination of prior art references or modification of the prior art is also required to establish obviousness, and this requirement is independent of the motivation to combine.

36. I have been informed that the asserted expectation must be grounded in what the prior art actually teaches, and cannot be based on generalized disclosures, mere possibility, hope, or hindsight reconstruction. I have also been informed that where the art is unpredictable or the petition for inter partes review fails to tie the prior art to the claimed results, Petitioner has not met its burden to prove reasonable likelihood of success.

V. SUMMARY OF OPINIONS

37. Based on my review of U.S. Patent No. 10,278,961 (Exh. 1001, the “’961 patent”) and its prosecution history (Exh. 1002), the other materials I have considered, and my knowledge and experience, my opinions are as follows:

- a. There are multiple reasons why animal models are suspect for use in predicting responses of other species, including humans, without rigorous validation. Reliance on results from one (or two) species, nearly always inbred, whether they are rat studies or mouse studies, or some other species, is potentially fraught with errors and clearly overly relied upon to predict the response in humans and thus inappropriate to present as prior art.
- b. Certain tests, such as an intraperitoneal glucose tolerance test, may have significant potential to generate artifacts and thus not present reliable animal study results.
- c. There are sufficient reasons why scale up models, such as the use of what is termed “BSA,” lack sufficient accuracy and therefore should not be relied upon to predict dosage

values.

- d. The reliance on rodent models cited in various references, including Ex 1004 – Turner and Ex 1007 – Feng, to establish that claims 1, 2, 5, 6 and 7 of the ‘961 patent are obvious is inappropriate given the deficiencies in using animal models discussed herein.
- e. There is insufficient public disclosure (patents, publications and the like) of the elements of claims 1, 2, 5, 6 and 7 before the effective filing date of the ‘961 patent to qualify as prior art capable of invalidating the mentioned claims.
- f. There is not a reasonable likelihood of success in the combination of prior art references or modification of the prior art to establish obviousness.

VI. OVERVIEW OF THE ’961 PATENT

38. The ‘961 patent (“Administration of Berberine Metabolites”) describes methods for administering certain metabolites of berberine, such as dihydroberberine and tetrahydroberberine, to humans to manage metabolic functions

including reducing fasting blood glucose, improving glucose tolerance, and increasing blood ketone levels, with potential therapeutic applications for conditions like diabetes, metabolic syndrome, dyslipidemia, obesity, and glucose intolerance. The patent explains that these metabolites may be more bioavailable and effective than berberine itself, and may be incorporated in various delivery forms (e.g., capsules, tablets, food or beverage products), alone or in combination with other compounds such as ketone sensitizers to promote ketosis. The '961 patent also covers dosing ranges (25 mg to approximately 800 mg of dihydroberberine), complex formulations (e.g., microemulsions, liposomes), and co-administration strategies to enhance efficacy and reduce side effects.

VII. LEVEL OF ORDINARY SKILL IN THE ART FOR THE '961 PATENT

39. I have been asked to provide my opinion regarding the level of ordinary skill in the art as of the effective filing date of the '961 Patent, which I understand to be April 19, 2016. My opinions would not change if April 19, 2017 were used as the relevant date because the level of ordinary skill and the pertinent scientific knowledge were substantially the same at either time. In assessing the level of ordinary skill in the art, I have considered the types of problems encountered in the art, the prior solutions to those problems found in prior art references, the rapidity with which innovations are made, the sophistication of the technology, the level of education of active workers in the field, and my own experience working with those

of skill in the art at the time of inventions.

40. Based on my education and experience, as described above and in my CV (Exh. 2164), as well as consistent with the subject matter of the '961 Patent and the prior art described below, it is my opinion that a person of ordinary skill in the art ("POSITA") during the relevant period would have held a Ph.D. or equivalent degree in biochemistry, pharmaceutical sciences, physiology, translational medicine, preclinical drug development, or a related biomedical field.

41. Alternatively, a POSITA could be a person with a master's degree with at least 2-3 years of experience in preclinical drug development. Such a person would have been familiar with "prior art," such as the limitations of extrapolating efficacy, pharmacokinetics, and dosing from rodent models to humans. A POSITA would know that administration of drugs and metabolites often involve the digestive tract and gut microbiota, which differ between species. A POSITA would be familiar with redox (reduction / oxidation) reactions and enzymatic reactions. Moreover, a POSITA would understand that positive findings in animal studies do not necessarily predict comparable results in humans, and that animal studies are generally used to generate hypotheses requiring confirmation in human subjects. A POSITA would further recognize that drug absorption and metabolism may be significantly affected by species-specific differences in gastrointestinal physiology, microbiota composition, enzymatic activity, and redox pathways. A POSITA would also

understand that body surface area (“BSA”) scaling and other animal-to-human dose conversion methods provide only rough estimates of safe starting doses and do not reliably predict an efficacious human dosage or therapeutic response. Accordingly, a POSITA would not reasonably expect efficacy, pharmacokinetic behavior, or optimal dosage ranges observed in rodents to translate directly to humans absent supporting human clinical data. Dr. Shebuski's proposed POSITA is inconsistent with the conclusions he reaches. *See* Exh. 1003 at ¶ 27. Moreover, a person possessing the ADME (Absorption, Distribution, Metabolism, and Excretion), pharmacokinetic, and toxicological knowledge described by Dr. Shebuski would understand the substantial uncertainty associated with predicting human efficacy and dosage from rodent studies alone.

VIII. CLAIM CONSTRUCTIONS UNDER C.F.R. § 42.104(b)(3)

42. It is my understanding that the parties agree that “managing glucose tolerance” from the “preamble” of the claim is to be interpreted as a claim element, or limitation of the claim. I generally agree with Dr. Shebuski’s characterization of “managing glucose tolerance” from paragraph 29 of his declaration, that it pertains to **both** fasting glucose levels and/or the ability to process ingested glucose. *See* Exh. 1003 at ¶ 29.

43. I understand that the parties have presented claim-construction positions in the related district court litigation and in this proceeding. I have reviewed those

positions to the extent necessary to understand the issues presented.

44. I have not been asked to opine on the proper legal construction of any claim term at this time. Rather, I have been asked to evaluate the scientific and technical issues relevant to the challenged claims, which I have done below.

IX. REBUTTAL TO DR. SHEBUSKI ON THE CHALLENGED CLAIMS

A. GROUND 1: Claims 1, 2, 5, 6, and 7 Are Not Obvious over Turner in View of Shaw

1. Claim 1:

a. A method of managing glucose tolerance in an individual comprising

45. In his report, Shebuski presents an excerpt from the Claim 1 preamble of the '961 patent, *viz*:

- a. "1. Claim 1: a. 1[Pre] A method of managing glucose tolerance in an **individual** [emphasis added] comprising:" Exh. 1003, ¶ 37.

46. As a first step is should be pointed out that the "individual(s)" presented in patent '961 is a human. This is sharp contract to Turner, which studies "rodent models" and component cells (e.g., L6 myotubes) and subcellular organelles (mitochondria) derived therefrom. *See* Ex 1004 at p. 2.

47. Shebuski then presents what he believes are appropriate teachings from Turner (see below) that exclusively involve what are described as the

aforementioned “rodent models” and components.

48. As will be show below, the use of Turner’s “rodent models” and measurements “in L6 myotubes and isolated muscle mitochondria” derived from rodents, and “high fat-fed rodents,” in berberine [BBR] and dihydroberberine [dhBBR] studies clearly and sufficiently differentiate Turner’s animal “rodent models” and other rodent components from the ‘961 [human] individuals. *See* Exh. 1004, at p. 1415 *et seq.* As will be discussed below, this differentiates Turner from the ‘961 patent to such an extent that Turner cannot be considered to be “obvious” prior art in regards to ‘961 Claims 1, 2, 5, 6, and 7.

49. Shebuski presents his contention that: “GROUND 1: Claims 1, 2, 5, 6, 7 Are Obvious over Turner in View of Shaw.” *See* Exh. 1003 at ¶¶ 36-37.

50. I respectfully disagree with this “obvious” contention of Shebuski, as discussed next. That is, I respectfully disagree that claims 1, 2, 5, 6 and 7 would have been obvious over Turner in View of Shaw to a person of ordinary skill in the art (a POSITA) at or before the priority date of the ‘961 patent.

51. In this section, Shebuski supports his position that these claims are “obvious” as follows:

52. In ¶ 37 Shebuski writes “Turner teaches a method of managing glucose tolerance in **rodent models**” [emphasis added]. *See* Exh. 1003, at ¶ 37. He cites Turner’s statement that “[t]he effect of a BBR derivative, dihydroberberine

(dhBBR), on ... glucose metabolism was examined in rodents fed a high-fat diet,” Exh. 1004 at 1, as well as Turner’s conclusion that “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.* Dr. Shebuski also cites Turner’s disclosure that “[i]n mice fed an HFD, treatment with dhBBR ... markedly ... improved glucose tolerance, compared with HFD controls (Fig. 3).” *Id.* at 2. In my opinion, the use of Turner to show the ‘961 patent claims 1, 2, 5, 6 and 7 are obvious is inappropriate for a number of reasons.

53. In the “Research Design and Methods” second of Turner, the feeding and dosing regimen is not exactly as presented by Shebuski.

54. To clarify, Turner stated that: “Animals were randomly assigned to receive either standard control rodent diet or a high-fat diet (HFD) to generate insulin resistance (9,10). 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 $100 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for the final 2 weeks of feeding.”

55. Note that having been fed for a number of weeks constitutes an extended period of pre-feeding time. The **pre-feeding** of the mice and rats with a high fat diet occurred for 8 of the 10 weeks, and 2 of the 4 weeks, respectively, prior to dosing with BBR and dhBBR, and then both the rats and mice were dosed with the test chemicals, BBR and dhBBR, for an additional 2 weeks **while still being fed the**

high fat diet.

56. No such pre-feeding or high-fat diets were employed with the human subjects in Examples 1-4 of the '961 patent.

57. The human subjects in Examples 1 through 4, did not consume multiple weeks of a high fat diet prior to tests. *See* Exh. 1001, 9:08-67.

58. The tests presented in the '961 patent lasted only 120 to 180 minutes (two to two and a half hours). *See Id.*

59. Shebuski uses misleading quotes, omitting important differentiating descriptions and interpretations, and thereby misrepresents Turner's research.

60. As presented in emphasis above, the first line in section IX ¶¶ 36-37 of the Shebuski declaration quotes the use of "rodent models." Although this is a correct quote, it is incomplete to the extent that it omits a description of the actual "rodent models" and thus is misleading. The descriptions may be clarified as follows:

- a. Turner indeed performed certain intraperitoneal glucose tolerance tests (depicted in FIG. 3), but on mice in specific, not rodents in general. Thus, the test was run on a single species, mice, and a single sex, male, and on a single sub-species, C57Bl/6J mice, preventing the generalization of results even to other sub-species, or species or sex, or rodents, let alone to

humans. HFD-fed rats were employed for other tests (see below) with some experiencing **undefined** “beneficial effects.” *See* Exh. 1004, at p. 4.

- b. Other tests, were performed in rats, where a hyperinsulinemic-euglycemic clamp was used (a method for measuring in vivo insulin sensitivity by artificially maintaining high blood insulin levels while simultaneously infusing glucose at a variable rate to hold blood sugar perfectly steady is performed). *See id.* at 3.
- c. The mouse glucose tolerance tests (shown in fig 3B; see annotated figure below), measured glucose levels during an **intraperitoneal** glucose tolerance test (apparently in mice). *See id.* at 4.

61. In Shebuski ¶ 39, pp. 19-20, Shebuski presents FIG 3B, reproduced from Ex - 1004, Turner. For ease in understanding the curves when viewing figure 3B of Turner¹ it has been annotated, next. The blood glucose level is shown on the Y axis. Time is presented on the X axis. CON, the lowest curve, is the control, where the mice are fed a normal rodent diet. HFD is where the mice were pre-fed a high fat

¹ Turner, BONERGE Exh. 1004, p. 4, FIG 3.B (center)

diet over a period of a total of 10 weeks as follows.

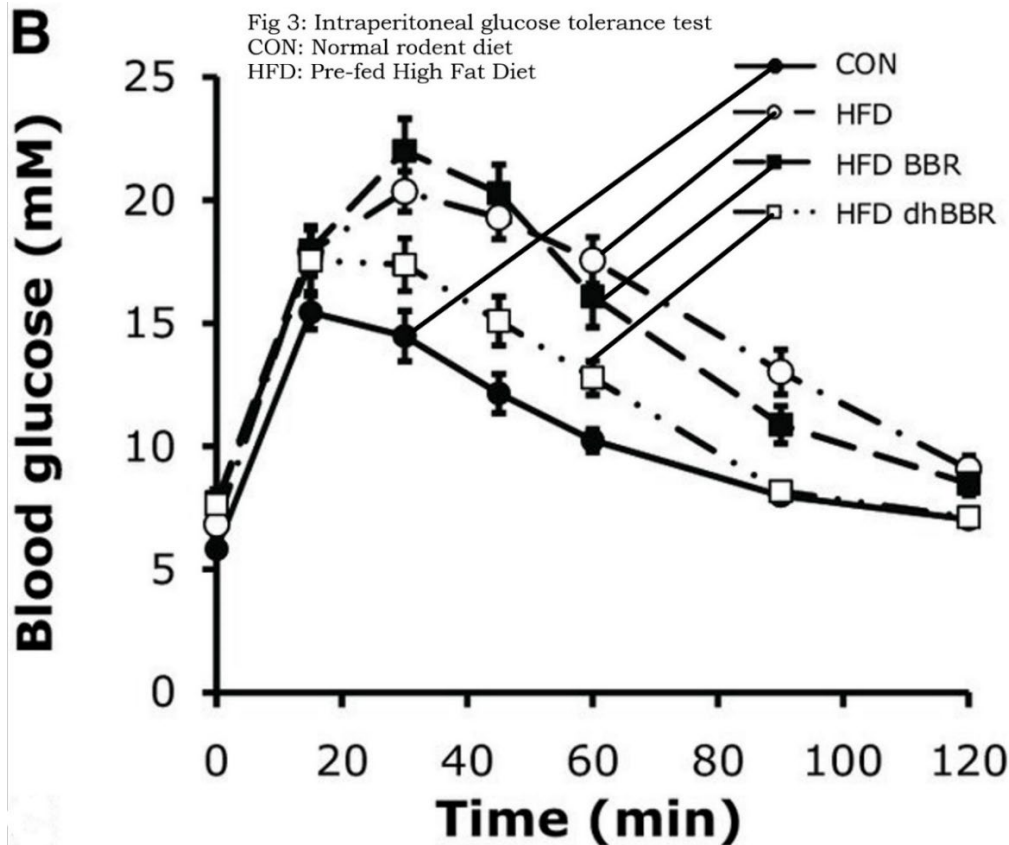
- a. “Animals were randomly assigned to receive either standard control rodent diet or a high-fat diet (HFD) to generate insulin resistance.” Exh. 1004, at p. 2.
- b. “Mice and rats were [pre-] fed for 10 weeks and 4 weeks, respectively and...” *Id.*
- c. “based on pilot testing for dhBBR in mice, BBR and dhBBR were provided in the HFD at a dose of $100 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for the final 2 weeks of feeding.”² *Id.*

62. Note the blood glucose level is artificially raised by this high fat diet pre-feeding action and it is at the highest level in the graphed results. The test HFD BBR, the pre-fed high fat diet mice which were then challenged with berberine, effectively matches the high level shown by the high fat diet alone, with HFD BBR glucose levels are actually higher than the glucose levels for HFD mice until 60 minutes into the test, that is, BBR has no real effect on the intraperitoneal glucose tolerance test when compared to the mice that had not been challenged with berberine. In the test HFD dhBBR, the pre-fed high fat diet mice which were then

² Turner, BONERGE Exh. 1004, p. 2, Section: Research design and methods/Animals

challenged with dihydroberberine only show a modest decrease in peak blood glucose compared to the control, and then only until about 60 minutes of the 120-minute test. After 60 minutes they match. There was no explanation as to why this effect vanished so quickly.

63. The results of these studies do not establish the claimed methods of the '961 Patent. None of the cited tests were performed under conditions that matched the claimed methods or the human studies described in the '961 Patent examples. Further, the cited studies do not demonstrate the type of glucose-management results that would have provided a POSITA with a reasonable expectation that administration of dihydroberberine to human individuals would achieve the claimed



outcomes.

64. In comparison to the studies presented in Turner, the Examples 1-4 presented in the '961 patent demonstrating the action of dihydroberberine:

- Were not run on rodents (mice or rats), or other non-human animals,
- Were run on humans,
- Did not involve the use of a hyperinsulinemic-euglycemic clamp,
- Did not involve gavage (force feeding of the subject by administering food and/or medication directly into the stomach using a small plastic or rubber tube) as a means of feeding

glucose to a subject, or employed gavage as a means for any feeding purposes (for example the Claim 6 dihydroberberine orally administered as at least one of a food product or beverage product), and not involved in, or for, any other purpose at all and is absent in the '961 claims as well.

- e. Were not performed using an **intraperitoneal** glucose tolerance test.

65. Of further note, Turner did not present controls that tested the blood glucose response to the administration of BBR or dhBBR minus the preceding HFD (that is, a control with administration of BBR or dhBBR to rodents that had been fed the normal rodent diet, not the pre-fed high fat diet).

66. Concerning the use of an **intraperitoneal glucose tolerance** test (an I.P. test), one may observe another difference, that this test effects different physiological responses of the subject and thus, with the potential to generate artifacts, and absent appropriate validations, an intraperitoneal glucose tolerance test **cannot** be considered directly predictive of results obtained by a standard oral glucose tolerance test. This is because admitting glucose through an intraperitoneal route alters the physiological response of the subject as it bypasses the GI tract of the individual being subject to the test, thereby creating a situation where digestive signals (meaning the gut-derived incretin hormones (like GLP-1 and GIP)) from the

GI tract are not secreted and thus other responses in the body do not occur. As demonstrated by Andrikopoulos et al., the route by which glucose is administered can materially affect the outcome of a glucose tolerance test. *See* Exh. 2154 at p. 10. After evaluating glucose tolerance testing in mice, the authors reported: that “[t]he next step was to determine the effect of route of administration on glucose tolerance by delivering a 2 g/kg glucose bolus either by intraperitoneal injection or orally via gavage after a 6-h fast (Figure 3). It is immediately clear that both the glucose and insulin excursions were significantly different depending on how glucose was delivered.” *See id.* The authors concluded that “one may expect that the intraperitoneal versus oral glucose delivery would result in different dynamics in the plasma glucose and insulin excursions, **which is exactly what [they] found.**” *See id.* at 15 (emphasis added). The authors further concluded that “the OGTT is a more sensitive technique” than the IPGTT. *See id.* at 16. Accordingly, a person of ordinary skill in the art would not reasonably rely on results obtained using intraperitoneal glucose administration to predict the results of oral glucose challenge testing.

67. From this one may only conclude that the results obtained from the Turner experiments are not directly comparable to the tests administered in the ‘961 patent.

68. As mentioned above, the rodents were pre-fed a high fat diet. This was done to generate insulin resistance.

69. Although the Turner publication presented research that was performed

subsequent to the high fat diet feeding of actual rodents, the tests other than the aforementioned glucose tolerance tests were not performed on the rodents, but rather were performed on subcellular muscle mitochondria isolated from the rodents' cells, and other cellular units.

70. To expand on this, many of the Turner experiments were performed on isolated myotubes and mouse embryonic fibroblasts (L6 myotubes), as well as the muscle-derived, sub-cellular organelle, mitochondria. None of the '961 claims 1, 2, 5, 6 and 7, nor any of the examples presented in the '961 patent involved isolated myotubes and mouse embryonic fibroblasts, or mitochondria, or any myotubes or any fibroblasts or any mitochondria derived from any species, nor are they even mentioned in the body of the '961 patent. The '961 patent involved human subjects ("...berberine metabolites, such as dihydroberberine... may be administered to manage blood glucose levels, increase ketone levels (e.g. blood concentration of ketones), and/or for therapeutic purposes in **humans**" [emphasis added]). *See* Exh. 1001 at p. 1.

71. Shebuski does not even present proof that the Turner cellular and subcellular experiments (i.e., the experiments employing mitochondria and/or L6 myotubes) are translatable biochemical processes occurring in the physiology of the whole entire organism, i.e., translatable to the rodents, the mice or rats, let alone translatable from biochemical processes occurring in mouse or rat mitochondria to

mouse or rat cells to mouse or rat organs or tissues to the physiologically functioning (living) whole mouse or rat in its entirety, and then to humans (and downwards to organs and tissues to cells to the subcellular level, that is, for a whole, functioning human to human organs or tissues, to human cells, to human mitochondria. Accordingly, there are far too many variables and uncertainties for such an extrapolation to be scientifically valid, or to create a reasonable expectation that the apparent results would be the same in humans.

72. Dr. Shebuski's declaration fails to acknowledge that in the Turner experiments rodents were **pre-fed a HFD** to induce insulin resistance whereas there is no comparable pre-feeding protocol reported for the subjects (humans) presented in the '961 patent. Thus, different administration procedures were followed, adding distance between the various studies and presenting unreliable conclusions.

73. Furthermore, many of the Turner experiments were performed on the mentioned cells or subcellular organelles derived from mice and/or rats that had been **pre-fed a HFD** before the animals had been sacrificed and the mentioned components removed for use in the experiments.

74. Although the '961 patent does mention "some implementation [where] one or more berberine metabolites may **be administered with**" [**meaning administered concurrently with**] certain additional compounds, it is distinctly different from pre-feeding or pre-fed protocols, namely:

- a. “In some implementations, one or more berberine metabolites may be **administered with** (emphasis added) one or more additional compounds. The additional compounds, such as ketone sensitizers, may be capable of independently inducing ketosis. The additional compounds may be utilized to maintain and/or promote ketosis in humans.” *See* Exh. 1001 at 2:7-12.
- b. “For example, the additional compounds may include one beta-hydroxybutyrate compound; butyrate; **short chain, medium chain, and/or long chain fatty acids or esters thereof** (emphasis added; these are components of fats); and/or combinations thereof which may be administered with a berberine metabolite, such as dihydroberberine.” *See Id.* at 2:12-17.

75. In contrast to the Turner publication, the ‘961 patent stresses that certain biochemicals commonly associated with fats, i.e., “fatty acids or esters thereof” may be “**administered with**,” (emphasis added) one or more berberine metabolites, but **NOT pre-fed** to the subjects, and certainly not pre-fed for a number of weeks or months as was done in the Turner experiments. Thus, the method of administration of such additional materials in Turner follows a distinctly different pattern from the ‘961 patent and is thus does not present an obvious teaching.

76. This further contributes to the rejection of Turner, as prior art to the ‘961 patent.

77. In addition, the description presented in the abstract of the ‘961 patent (last two lines), and also presented in a number of other locations in the patent, is a description that, again, differentiates the approach taken in the ‘961 patent from the approach presented by Turner. *See id.* at p. 1. This is a clear difference because, in the ‘961 patent, “one or more other compounds,” are administered **with** the test compounds, that is, “...berberine metabolites may be **administered with** one or more other compounds,” where the expression “**administrated with**” is used in relation to “short chain, medium chain, and/or long chain fatty acids or esters thereof.” *See id.* at 2:7-17 (emphasis added). This procedure of “administered with” or words to that effect, is found in a number of locations in the ‘961 patent plus claims 14, 18, 19 and 20.³

78. The best estimate of timespan for “**administered with**” is the 120 minutes as described in the examples presented in the ‘961 patent.

79. At no point does the ‘961 patent indicate or suggest the test subject was subjected to a **pre-fed, high fat diet**.

80. Unlike the Turner document, at no point does the ‘961 patent indicate or

³ See Exh. 1001, 2:7-17, 3:8-25, 3:23-25, 4:10-17, 6:7-21, and claims 14, 18, 19 and 20.

suggest tests were performed on sub-cellular organelles (e.g. mitochondria) or cells or sub-cellular structures, or cellular structures derived from the test subject or a test subject that had been pre-fed a high fat diet.

81. Furthermore, the conclusions drawn in the Turner document relating to tests run with *Rattus norvegicus* (rat) L6 myotubes⁴ and/or isolated mitochondria present no proof that the results are translatable to human studies.

82. Accordingly, Turner does not disclose the claimed methods of the '961 Patent and does not provide a reliable basis for predicting the results of the human studies described in the '961 Patent. The substantial differences in species, experimental design, metabolic conditions, and testing methodologies significantly limit the relevance of Turner to the claimed human administration of dihydroberberine.

83. Moreover, there are additional reasons to further discount the relevance of the Turner article as being prior art to the '961 patent. That is, simply stated, certain experiments presented in the Turner article were not only run on isolated sub-cellular organelles (mitochondria) or cell groupings (the L6 myotubes) they were not even run on organelles or cell groups of human origin. The experiments were not even

⁴ See Exh. 2155 at p. 2 ("L6 cells fuse in culture to form multinucleated myotubes and striated fibers")

performed on genetically more closely-related primate-derived sub-cellular organelles or cell groups, but rather run on materials derived from rodents, rats and mice.

84. There are numerous articles presenting arguments as to why the use of animal models is an inaccurate and inappropriate to predict human responses. That animal models are poor predictors of human responses is not a recent concept but rather may be traced back a thousand years.

85. As noted by Bracken in 2008:

The concept that animal research, particularly that relating to pharmaceuticals and environmental agents, may be a poor predictor of human experience is not new. A thousand years ago, Ibn Sina commented on the need to study humans rather than animals¹, and Alexander Pope's dictum 'The proper study of mankind is man' is well known and has been widely cited². Pharmacologists, in particular, have long recognized the difficulties inherent in extrapolating drug data from animals to man.^{3,4} Given the large number of animal studies conducted, it would be expected that some animal experiments do predict human reactions. For example, penicillin was observed to protect

both mice and humans from staphylococcal infections⁵, and isotretinoin ('Acutane' *sic* Accutane) causes birth defects in rabbits and monkeys as well as in humans (although not in mice or rats)⁶. By contrast, corticosteroids are widely teratogenic in animals but not in humans⁷, and thalidomide is not a teratogen in many animal species but it is in humans.⁸ Recent experience in a phase 1 study of the monoclonal antibody TGN 1412 resulted in life-threatening morbidity in all six healthy volunteers, reflecting inadequate prediction even in non-human primates of the human response⁹.

See Exh. 2156 at p. 1.

86. In the aforementioned Bracken article, there are numerous arguments presented as to "why animal studies may not predict human reactions." *Id.* As an example they present certain groups of animal studies and whether they were predictive of human trials. They were not predictive:

In three of the research areas the animal studies and human trials were substantially discordant; in three others the results were essentially similar. In all areas of research, however, major methodological limitations of the animal

research and evidence of widespread publication bias were identified.

See id.

87. Taken in the aggregate, with the Turner experiments being quite different from the '961 examples, and, absent concrete proof that the non-human sub-cellular organelle and cell culture BBR, or dhBBR, or other BBR metabolites experiments of Turner are predictable and translatable to human response, the Turner experiments cannot be presented as proof that Claims 1, 2, 5, 6, 7 are obvious over Turner in view of Shaw.

88. Concerning BSA calculations as presented by Shaw (*See* Exh. 1005), an article by Blanchard et al. may be consulted, where the use of BSA calculations to convert animal dosing levels to human dosing levels, is severely criticized as antiquated and incorrect, particularly as to active dosing levels. For example, there is the following excerpt:

89. "A thorough review of the literature reveals that **BSA conversions are based on antiquated science and have little justification in current translational medicine** (emphasis added) compared to more advanced allometric and physiologically based pharmacokinetic modeling. Misunderstood and misinterpreted use of BSA conversions may have disastrous consequences, including underdosing leading to abandonment of potentially efficacious

investigational drugs, and unexpected deadly adverse events. We aim to demonstrate that recent recommendations for BSA are not appropriate for animal-to-human dosage conversions and use pharmacokinetic data from resveratrol studies to demonstrate how confusion between the "human equivalent dose" and "pharmacologically active dose" can lead to inappropriate dose recommendations. To optimize drug development, future recommendations for interspecies scaling must be scientifically justified using physiologic, pharmacokinetic, and toxicology data rather than simple BSA conversion.” *See* Exh. 2157, at p. 1.

90. Petitioner’s reliance on Shaw is substantially weakened. As discussed below, Shaw likewise does not provide an appropriate basis for predicting the claimed human methods. In particular, Shaw relies on FDA guidance directed to **“deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities in adult healthy volunteers”** and **“recommends a standardized process by which the MRSD can be selected.”** *See* Ex 1008, at p. 1. That guidance concerns the selection of a safe starting dose for an initial human clinical trial, not the determination of an efficacious human dose or the prediction of therapeutic effectiveness.

91. The entire excerpt is bolded to differentiate it from the ‘961 patent where no aspect of the excerpt is presented at any significant level in the patent. The FDA guidance excerpt is directed to the selection of a maximum recommended starting

dose (“MRSD”) for first-in-human studies and incorporates significant safety considerations intended to minimize risk to human subjects. The guidance therefore addresses the determination of a conservative starting dose for a new molecular entity, rather than the identification of a therapeutically effective dose. In contrast, neither the ‘961 Patent nor its claims are directed to selecting an MRSD or applying the safety factors described in the FDA guidance. Accordingly, the FDA guidance addresses considerations that are materially different from those presented by the challenged claims.

b. 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

92. In Section IX ¶ 38, p. 19 of his declaration (*See* Exh. 1003), Shebuski states that “Turner discloses potentially conducting clinical studies.” Oddly, Turner never mentions the phrase “clinical studies” so it is not clear why Shebuski makes this comment. Furthermore, in contrast, Claim 1 of the ‘961 patent does not claim clinical studies as a limitation, nor are clinical studies mentioned in the body of the ‘961 patent, although prior studies involving bioavailability of traditional berberine (not dihydroberberine) “in animal models” is mentioned (*See* Exh. 1001, at 01:33-

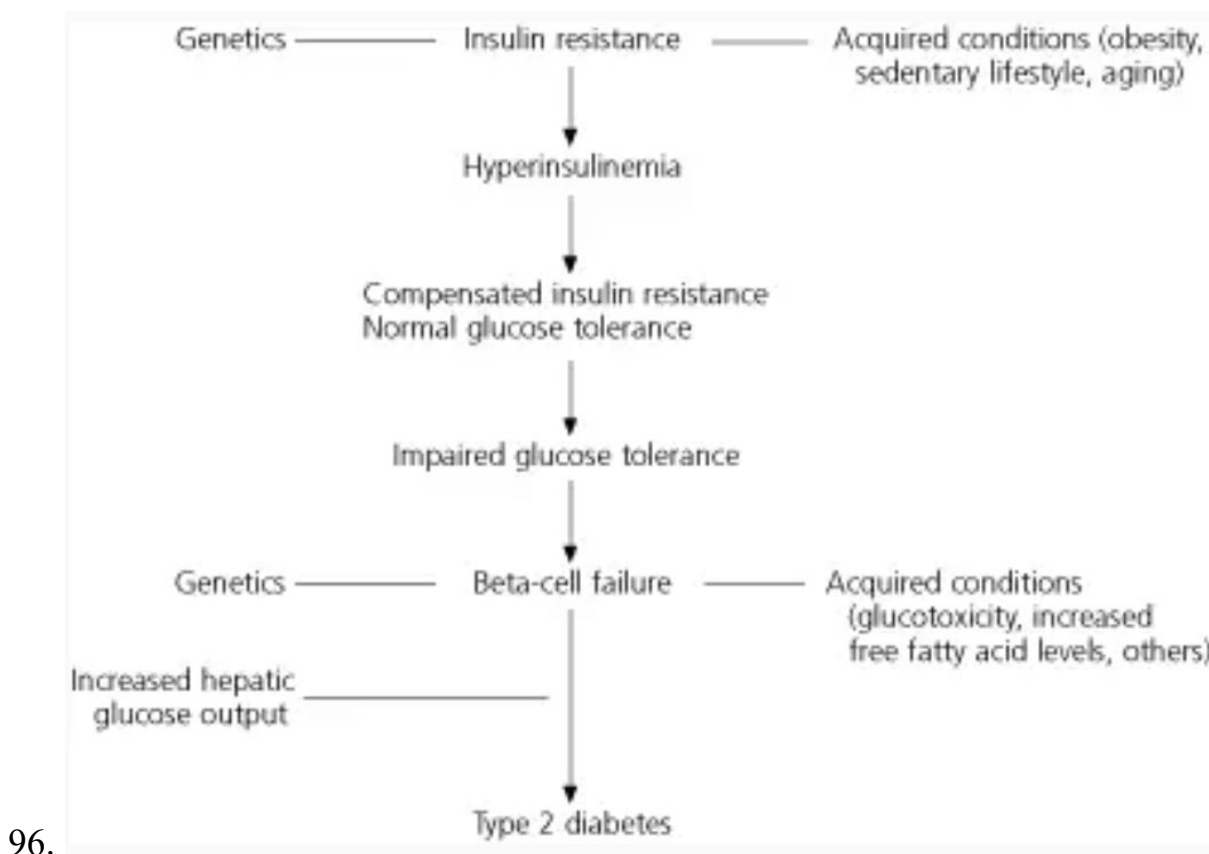
38). Thus, Shebuski's comment has no merit as an example of prior art obviousness.

93. Further on in ¶ 38, p. 19, Shebuski references Turner, which states that “dhBBR represents an attractive potential therapy for the treatment of type 2 diabetes and other components of the metabolic syndrome.”. *See* Exh. 1004, at p. 4.

94. The “detailed Description” section of the ‘961 patent does mention that “In some implementations, administration of a pharmaceutically effective amount of berberine metabolite(s) (e.g., dihydroberberine and/or tetrahydroberberine) may be therapeutic to humans with diabetes...” (Exh. 1001, at 03:63). However, no limitations mentioning treatment of diabetes or type 2 diabetes and other components of the metabolic syndrome are present in Claim 1 or any of the claims in the ‘961 patent.

95. Managing glucose tolerance (which is what is presented as a limitation in Claim 1 and all claims dependent upon Claim 1, since, by definition under patent law, a dependent claim incorporates all the elements and limitations of the previous claim it refers to) is not the same thing as managing type 2 diabetes. Glucose tolerance is a physiological response that describes at least in part how well your body processes the simple sugar, glucose (dextrose), and the glucose tolerance test is a diagnostic tool to measure if the processing is normal (≤ 139 mg/dL after 2 hours) or impaired (140 to 199 mg/dL after 2 hours). If impaired, the condition is referred to as prediabetes, a risk factor, but not diabetes. In contrast, type 2 diabetes

is the actual clinical diagnosis where the blood sugar levels are chronically at a high level due to the inability to properly use or make insulin, at a higher glucose level than the others (level chronically ≥ 200 mg/dL). *See* Exh. 2158, at p. 1-5. The differentiation is diagrammed in Rao and clearly shows the differences; Figure 1 from Rao, Etiologic sequence for the development of type 2 diabetes. *See* Exh. 2159, at p. 3.



97. Thus, the two conditions are separate clinical entities and should not be conflated.

98. In that light, Shebuski's comment has no merit as an example of prior art

obviousness.

99. In section IX ¶ 39, pp. 19-20 of his declaration, Shebuski states that “Turner discloses the pharmaceutically effective dosage amount for managing blood glucose levels in rodents,” but Shebuski does not state the complete feeding history of the rodents being dosed and the exact chemical administered to the rodents being treated. *See* Exh. 1003, at ¶ 39. Absent the complete feeding history, one can be readily misled. Not mentioning this information tends to obscure the fact that Turner is not administering dhBBR to rodents simply fed a high fat diet at the point in time of the test but rather pre-fed a high fat diet fed over a two-week period prior to the tests, as discussed above.

100. Furthermore, these Turner tests were not performed on humans.

101. It is humans who are the test subjects in the ‘961 patent, and the “individual” in claim 1 of the ‘961 patent, and none of the human test subjects were subjected to a long-term pre-feeding of a high fat diet.

102. Shebuski presents Shaw’s explanation as to “how to use the body surface area (BSA) normalization method to translate drug dosage from animals to humans.” *See* Exh. 1003, at ¶ 40. As presented below and elsewhere, I disagree with this assessment.

103. Shaw is a 2008 publication titled “Dose translation from animal to human studies revisited.” *See* Exh. 1005, at pp. 1-3. The Shaw paper presents a

position that “The animal dose should not be extrapolated to a human equivalent dose (HED) by a simple conversion based on body weight... [but that] [f]or the more appropriate conversion of drug doses from animal studies to human studies, we suggest using the body surface area (BSA) normalization method... 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.” *See id.* at p. 1.

104. Simply stated, Shaw recommends “the body surface area (BSA) normalization method” as the method to translate drug doses from animal studies to humans.

105. Shebuski inappropriately presents Shaw to support Turner as follows: “Claims 1, 2, 5, 6, 7 Are Obvious over Turner in View of Shaw.” Shebuski presents Shaw as though the approach presented by Shaw is settled clinical science. Not only is the Shaw approach not settled science, but there are multiple publications that demonstrate that the Shaw BSA approach is flawed.

106. One obvious reason the Shebuski position is flawed is that Turner did not perform any animal studies equivalent to the human studies presented in the ‘961 patent. Rather, as pointed out above, Turner performed certain studies on rodents, and other studies on cell groupings and the sub-cellular organelle, mitochondria, all derived from animals, but not the animals themselves. Thus, for this reason alone Shaw has no supporting relevance to the Shebuski contention that “GROUND 1:

Claims 1, 2, 5, 6, 7 Are Obvious over Turner in View of Shaw.”

107. As stated above, the Shaw is not even settled science; thus, it cannot be presented as teaching or supporting prior art.

108. The Shaw contention that the body surface area (BSA) normalization method is disputed by multiple publications.

109. One article that disputes the use of BSA normalization is the article written by Frazier and Price that addresses limitations on BSA calculations imposed by pharmacokinetic factors. *See* Exh. 2160, at pp. 1-7. Frazier and Price recognize that a body surface area (BSA)-based dosage regimen may have some historic interest as it has been used “for several decades” is important to minimize excessive drug exposure and may occasionally be appropriate. *See id.* at p. 1. However, using dogs as an example, they then state the following in the section titled “Pharmacokinetic Processes and the Effect of Body Size Absorption”:

110. “Almost all drugs are absorbed by passive diffusion; therefore, drug absorption is a function of the physicochemical properties of the drug rather than physiologic processes. To our knowledge, the surface area for diffusional absorption has not been shown to change in proportion to metabolic rate or BSA. The extent of drug absorption in dogs of different body size should be similar regardless of whether the drug is administered on the basis of body weight or BSA.” *See id.* at p. 2.

111. Excretion is another factor, not even addressed by Shebuski, and will affect the physiological response. *See id.* at p. 3.

112. “The concentration of a drug in blood over time (AUC) [Area Under Curve = Area under the plasma drug concentration versus time curve] is a function of the total clearance by all eliminating organs.” *See id.*

113. Age and disease are additional factors not even addressed by Shebuski. *See id.*

114. Various published attempts at BSA predictions were found to be faulty (see reference to creatinine clearance and, as an example, CDDP (cisplatin) vs. carboplatin [platinum-based drugs] with an elimination half-life of 70 hours and 2-hour half-life in humans and species-dependent variations). It is not even known if the correlations are predictive within a species: “Whether unbound platinum clearance is proportional to BSA for members of a single species is not known.” *See id.*

115. Excretion rates vary from species to species, and may not even be known within a species, thus negating even the best BSA estimates. Furthermore, for some drugs “both the rate of formation of the active metabolites and the excretion rates of the parent compounds and metabolites should be considered for dose normalization.” *See* Exh. 2160, at p. 4. This is especially true in the current discussion since dhBBR is converted to BBR at some point in absorption and/or

post-absorption process. Absorption, distribution, excretion, metabolism, as well as other variables, that make BSA calculations suspect and unreliable, as further addressed in Frazier and Price and are all included here by reference. *See id.* at pp. 1-7.

116. Thus, considering variations in the above, including pharmacokinetics, reliance of traditional, but outdated BSA equations, calculation inconsistencies and genetic and metabolic variations, Shaw cannot be relied upon at any level as prior art.

117. Furthermore, Shaw did not perform, nor did anyone else perform, the calculations based upon Shaw's publication, for dihydroberberine before the priority date of the '961 patent. Thus, the Shaw calculations presented by Shebuski (*See* Exh. 1003, at ¶¶ 40-43, pp. 20-21) are after-the-fact and thus could not be used in a predictive capacity. The conclusion is that the calculations are thus not relevant and cannot be presented as prior art.

118. Thus, this is a strong indication that the BSA calculations performed by Shebuski are inappropriate as a method to compare Turner's results with the '961 patent results in any comparative or quantitative fashion.

119. In this light, the Shebuski calculations based upon Shaw (Exh. 1003, at ¶¶ 40-43, 48-49, 52- 57) are flawed in that there is no validation to demonstrate that they present values that accurately predict the values presented in the '961 patent,

that is, the appropriate “Pharmacologically Active Dose [PAD]” as described next.

120. This conclusion is supported by the FDA guidance in Exh. 1008, at p. 15 under “VIII. STEP 5: CONSIDERATION OF THE PHARMACOLOGICALLY ACTIVE DOSE [PAD]” where the FDA states the following: “Selection of a PAD [Pharmacologically active dose] depends upon many factors and differs markedly among pharmacological drug classes and clinical indications; therefore, selection of a PAD is beyond the scope of this guidance.”

121. Not only is the selection of a PAD beyond the scope of the FDA guidance, it is beyond the position presented in the Shebuski report.

122. In summary, for the reasons presented above, these BSA calculations are irrelevant and should not be considered as prior art.

123. In ¶ 41, Shebuski further presents Shaw’s advocacy to the use of the BSA method which, for reasons already stated above and elsewhere, I believe are not applicable. *See* Exh. 1003, at ¶ 41.

124. In ¶ 42, Shebuski states that “Turner discloses that “In mice fed an HFD, treatment with dhBBR (100 mg•kg⁻¹•day⁻¹) markedly ... improved glucose tolerance, compared with HFD controls (Fig. 3).” Exh. 1004, Turner at 1415.” *See* Exh. 1003, at ¶ 42.

125. However, Shebuski neglects to state that BBR or dhBBR were provided along with the HFD for an entire 2 weeks at a dose of 100 mg•kg⁻¹•day⁻¹. That is,

they were pre-fed both the high fat diet and pre-fed BBR or dhBBR simultaneously over a two-week period. In contrast, with the '961 patent, there was neither a pre-feeding of a HFD nor a pre-feeding of berberine nor dihydroberberine. With the '961 patent, the subjects were administered the BBP or dhBBR and then took the glucose tolerance test, with no indication of delay or high fat diet protocol. These differences significantly limit the relevance of Turner to the claimed methods and undermine any assertion that Turner discloses or renders obvious the human administration protocols described in the '961 Patent.

126. In ¶ 43, p. 21 Shebuski presents the BSA conversion results, which I believe is inappropriate as stated above and elsewhere. *See id.* at ¶ 43.

c. A POSITA Would Not Have Been Motivated to Combine Turner and Shaw with a Reasonable Expectation of Success

127. In ¶ 44, p. 21 Shebuski introduces his opinion on this subject. *See id.* at ¶ 44.

128. It is my understanding that the motivation to combine element of the obviousness analysis is separate and distinct from the reasonable expectation of success element. Dr. Shebuski appears to have conflated them, which, I understand is incorrect.

129. Here, at Shebuski ¶ 44, Shebuski continues the apparent attempt at conflation and actually presents a statement from Turner that is not presented in the

‘961 patent, that is, that “dhBBR can be effective for human diabetes treatment.” *See id.* at ¶ 44. Turner never makes this statement. In actuality, what Turner stated is the following:

130. “These findings indicate that dhBBR is in essence an effective vehicle for delivering BBR to the circulation, substantially reducing the oral dose required for beneficial metabolic effects. As BBR has been shown to improve clinical symptoms in patients with type 2 diabetes (4) and dyslipidemia (5), and undesirable side effects have been reported for several popular anti-diabetic drugs (25), dhBBR represents **an attractive potential therapy for the treatment of type 2 diabetes** (emphasis added) and other components of the metabolic syndrome.” *See* Exh. 1004, at p.4.

131. Turner’s speculation that “...dhBBR represents **an attractive potential therapy**” (emphasis added) (Exh. 1004, at p. 4) is certainly not the same thing as Shebuski’s misquoting Turner by replacing “attractive potential therapy for the treatment of type 2 diabetes” with “**effective** for human diabetes treatment” (Exh. 1003, at ¶ 44. (emphasis added)) to describe the same Turner statement. Turner does not state, or imply, dhBBR treatment is effective, nor does he mention humans in this regard. *See* Exh. 1004, at p. 4. Thus, Shebuski is inferring something never stated or implied by Turner. Furthermore, the ‘961 patent does not specifically claim diabetes treatment of any type but rather “**a method of managing glucose tolerance**

(emphasis added).” Thus, this exaggeration is inappropriate to be presented as prior art.

132. That said, I also further disagree with Dr. Shebuski’s analysis because of the reasons stated above that relate to the inappropriate use of Turner’s so called rodent models, only some of which involve rodents while others involve organized cells and mitochondria derived from rodents, and the presented inappropriate support “in light of” BAS calculations that have only a weak and speculative basis for being predictive at best, and may not be predictive at all since it does not take into account the variables summarized above.

133. In ¶ 45, p. 22, Shebuski presents Turner’s teaching as a motivation “to launch clinical studies of dhBBR for managing glucose tolerance in humans, with reasonable expectation of success.” This was not stated by Turner but is speculated by Shebuski. *See* Exh. 1003, at ¶ 45.

134. Shebuski then continues in ¶ 45, pp. 22-23 and defends this speculation by stating “This is because the studies in Turner were conducted on one of the most commonly used animal models for type 2 diabetes research. Moreover, 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.” *See id.*

135. In ¶ 46, pp. 23 Shebuski attempts to further bolster his animal model

beliefs by stating “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.” In defense of this position he references Exh. 1011, King at 881-882 “(outlining some of “the most commonly used models for type 2 diabetes” in Table 2) & Table 2.” However, being common does not make the position universally correct. This “reasonable expectation of success” is a fallacy, not the least of which is the choice of the study animals by Turner. *See id.* at ¶ 46.

136. In opposition to Shebuski’s position, a number of authors, such as Hartung, have cast doubts on the overly optimistic belief on reliability of the transferability of animal studies to human treatments. *See* Exh. 2030. Except in retrospect, it is often not possible to employ animal models to accurately take the animal results and directly extrapolate them to results of the same treatment in humans. The entire Hartung paper is included here by reference, but some pertinent extracts from Hartung are:

- a. **No model is perfect.** Shebuski refers many times to his personal experience working with animal models, but is light on mentioning the drawbacks of drawing conclusions from such studies. Turner’s and other references’ “models” are mentioned in a number of places in Shebuski’s report (e.g., ¶¶ 25, 37, 38, 45, etc.). However, concerning animal models recall the

following caveat quoted in Hartung: “The famous NIH pharmacologist Bernard Brodie coined it already in 1964: “...it is often a matter of pure luck that animal experiments lead to clinically useful drugs.”” *See id.* at p. 2. There is no reason presented in the Shebuski report to make one believe that that “pure luck” does not apply to the current purported prior art supposition and thus results of tests from such laboratories as Turner’s should not be presented as prior art.

- b. **“Species-differences** – rarely can the same experiment be performed both on humans and on experimental animals; where this is possible (e.g. skin irritation (York et al., 1996; Basketter et al., 2004)) a correlation of about 60% is found.” *See id.* In an historical example presented by Hartung, this is unfortunately exemplified by anti-CD28 tests which were perfectly safe in 100s of monkeys, but killed six human volunteers within hours. *See id.* In the current context, Shebuski’s so-called POSA (POSITA) motivation to apply the teaching of Turner “because the studies in Turner were conducted on one of the most commonly used animal models for type 2 diabetes research,” that is, in this case, rats, is actually a major negative criticism of those researchers in

general, and Turner in specific, since the work is overly focused on testing just two species, rat and mouse, and just one variety and sex of each (Male C57Bl/6J mice (6–8 weeks old) and male Wistar rats) at that. As just noted, obtaining results from one species, whether they be monkey studies or rat studies, is clearly overly relied upon to predict the response in humans and potentially fraught with errors.

- c. **“Pharmaco- and toxicokinetics of substances differ between animals and humans** – humans are not 70 kg rats [attempts at BSA estimations notwithstanding]: there are tremendous differences to all laboratory animal species, e.g. in metabolic rates, food and water intake, pH in the gut, body temperature, metabolism of xenobiotics with regard to capacity, velocity and metabolites formed, body fat distribution, elimination routes, carrier proteins / protein binding, defence (defense) mechanisms, life span.” *See id.* Safety factors of 100 are used. I notice that Shebuski did not present such large, but toxicologically appropriate, cautionary numbers.
- d. **“In-bred strains** – the broad use of inbred strains has helped to reduce the variability of experimental results.” *See id.* But by the

same token, since only one specific, inbred variety of mouse and one inbred variety of rat were used by Turner (and by others) it is not even known if the experimental results are translatable from rat variety to rat variety, or mouse variety to mouse variety let alone from rat (or mouse) to human. Thus, the Turner animal studies presented by Shebuski should not be considered as presenting prior art.

- e. **“Young animals** – typically, for cost and logistic reasons, young animals are used for experiments.” *See id.* Older animals (humans too, as is well-known) tend to have more health issues yet the validity of using only younger animals in the studies presented by Shebuski was not addressed in his report. Thus, the animal studies presented by Shebuski should not be considered as presenting prior art.
- f. **Restriction to one sex** – Hartung notes that restricting studies to a single sex reduces the spectrum of sensitivities under evaluation and may fail to account for sex-based differences in drug and toxic responses. *See* Exh. 2030, at p. 2.
- g. **Group sizes** – Animal studies often employ the smallest possible group sizes, frequently without a power analysis sufficient to

determine whether statistically significant results can reasonably be expected. *See id* at pp. 2-3.

- h. **Cost** – Maintaining adequate animal numbers and employing qualified staff is extremely costly. As a consequence, the number of replicates and repetitions is typically limited. *See id.* at p. 3.
- i. **Unrealistic dosages and exposure durations** – Hartung observes that animal studies frequently employ high-dose treatments and exposure conditions that do not realistically reflect human exposures and may produce effects that are not relevant to the human condition. *See id.*
- j. **Many health effects are multi-factorial** – Many human diseases and health effects result from numerous genetic, psychological, social, dietary, and environmental factors, whereas animal disease models are often based on only a single artificial cause. *See id.*
- k. **Animals are stressed** – Hartung notes that laboratory animals are subject to numerous sources of stress, including transportation, handling, housing conditions, group changes, and experimental procedures, all of which may influence study outcomes. *See id.*

- l. **Adaptive responses of animals are underestimated** – Hartung explains that animals may adapt to experimental conditions, thereby influencing subsequent responses and potentially confounding interpretation of study results. *See id.*
- m. **Proprietary data** – data may not be available, preventing a full assessment.

137. The list and discussions in the above Hartung reference continue further and are long and compelling. They are included by reference.

138. From these and other examples one should readily conclude that the references presented by Shebuski, especially from Turner with or without Shaw, do not present prior art in relation to the '961 patent.

139. As already stated, Shebuski presents the concept that “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**.” *See* Exh. 1003, at ¶ 46, p. 23 (emphasis added). Shebuski presents Exh. 1011, King, to support his position of “The use of animal models in diabetes research.” The '961 patent does not specifically claim a method of treating diabetes, but rather addresses “a method of managing glucose tolerance.” ('961, Claim 1)

140. King presents animal models but does not present studies involving either berberine or dihydroberberine.

141. The use of animal models has already been discussed in this report. See comments under Hartung and Bracken that not only do not support Shebuski's position(s) but actually discredit Shebuski's position(s).

142. Furthermore, once again, it must be stressed that the '961 patent does not involve diabetes of any type, nor a treatment to improve insulin resistance, but rather "A method of managing glucose tolerance in an individual [human]." *See* Exh. 1001, claim 1. Thus, the presentation of type 2 diabetes or insulin resistance treatments by Shebuski is another straw man argument and is not pertinent as prior art and should be disregarded.

143. And once again, none of this should be presented "in light of" the flawed Shaw studies which are clearly not demonstrated to be valid for predicting the dosages.

144. In ¶ 47 Shebuski presents Exh. 1009, Chen at 1822-23 in defense of his contention of the appropriateness of use of "rodent studies launch clinical studies that yield successes." However, this contention is not valid. Chen studied patients fed berberine (not dihydroberberine). Chen's research involved irritable bowel syndrome quality of life events, mostly involving gastrointestinal motility. The research measured such related variables as diarrhea (see Chen, table 2), abdominal pain (see Chen Fig. 4) and frequency of urgent need for defecation (see Chen Fig. 3.) and at no time measured a glucose tolerance test response, whether to

hydroxybenzene or not. At no point in Chen are studies concerning dihydroberberine mentioned or implied, nor were the subjects pre-fed the Turner high-fat diet prior to a glucose tolerance test. Chen's evaluation was basically a clinical anti-diarrhea and gastroenteritis study. Chen did not present "rodent studies [that] launch clinical studies that yield successes." Thus, Chen is not appropriate to be presented as prior art.

145. Thus, my conclusion continues that is that Shebuski has not been persuasive and that Claim 1 should not be rejected, since the so-called prior art references, alone or in combination or "in light of" do not make the invention obvious prior art to a person having "ordinary skill in the art."

146. In ¶ 48 Shebuski presents Shaw once again and contends, without support, that "Shaw discloses that the BSA normalization method is the "most appropriate" method to translate drug dosage from animals to humans. Exh. 1005, Shaw at 661." Shaw's calculations have already been addressed previously in the current report and shown not to be appropriate as persuasive prior art relative to the '961 patent and does not make Claim 1 of the '961 patent, or other aspects of the '961 patent, obvious to a person having "ordinary skill in the art." Refer to the prior sections for that discussion. *See* Exh. 1003, at ¶ 48.

147. Continuing in ¶ 48 Shebuski presents the following on FDA guidance. "Using BSA method for converting drug doses from animal studies to clinical trials

is also recommended by the FDA Guideline document (“normalization to body surface area has remained a widespread practice for estimating an HED based on an animal dose.”). Exh. 1008, FDA Guidance at 6.” *See id.*

148. However, note that this is an inappropriate comparison based upon the introduction of the FDA document. That is that Shaw is not appropriate if the first line in the introduction of the referenced FDA document is consulted that presents guidance for “deriving the maximum recommended starting dose (MRSD) for first-in-human clinical trials of new molecular entities in adult healthy volunteers, and recommends a standardized process by which the MRSD can be selected.” *See* Exh. 1008, at p. 1.

149. The ‘961 patent does not present starting dose for first-in-human clinical trials.

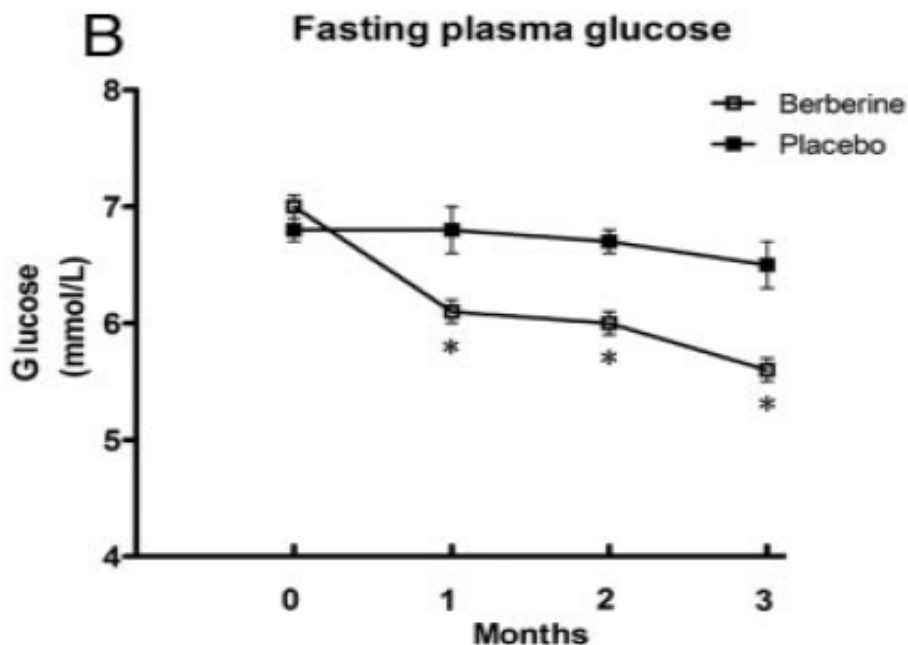
150. FDA PAD Guidelines have also been discussed elsewhere in the current report.

151. In ¶ 49 Shebuski further discusses PAD estimates and attempts to relate these estimates to Exh. 1006 Zhang and Exh. 1010 Liu. *See* Exh. 1003, at ¶ 49. Since the BSA calculation is discredited to an informed POSITA (*see* Blanchard and Frazier and Price discussions in this report – Exhs. 2157 and 2160), adding Zhang and Liu do not act to rehabilitate BSA calculations, or by adding articles presented in the reference sections of Zhang and Liu. Thus, to a POSITA, these estimates do

not constitute applicable prior art.

152. In ¶ 50, Zhang is further presented, that it, in addition to the preceding sections of his report, Shebuski relies heavily on Zhang (Exh. 1006) for his third (Ground 3) obviousness contentions. *See* Exh. 1003, at ¶ 50. At Petition (Paper 2), p. 43, Petitioner cites Zhang and contends that diabetic patients treated with berberine (but not dihydroberberine) for three (3) months allegedly showed a significant improvement in fasting plasma glucose levels compared with placebo. Petitioner pointed to Fig. 3B of Zhang in support. Fig 3B is Zhang appears as follows:

a. Exh. 1006, p. 5 (Fig. 3B) (below).



b. Fig. 3B of Zhang (shown immediately above), seems to be based

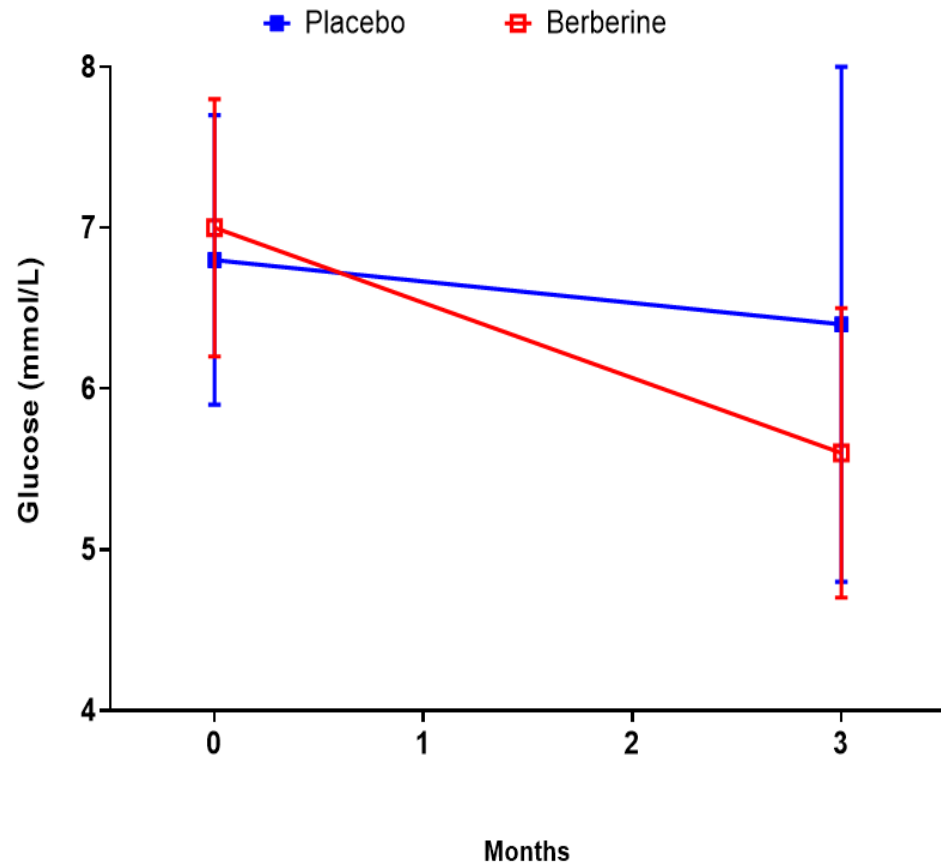
on the data contained in Table 1 of Zhang, but does not appear to accurately represent that data:

TABLE 1. Baseline and 3-month clinical characteristics of berberine and placebo groups

	Berberine			Placebo ^a			<i>P</i> value ^a
	Before	After	<i>P</i> value ^b	Before	After	<i>P</i> value ^b	
No. (male/female)		58 (30/28)			52 (31/21)		
Age (yr)	51 ± 9	51 ± 10					
Current smokers		14			20		
Alcohol use		4			15		
Body weight (kg)	68.7 ± 11.3	66.4 ± 11.8	0.000	71.8 ± 11.2	70.5 ± 11.0	0.000	0.034
BMI (kg/m ²)	25.2 ± 3.1	24.3 ± 3.2	0.000	25.9 ± 3.8	25.4 ± 3.6	0.000	0.021
Waist to hip ratio	0.91 ± 0.06	0.89 ± 0.06	0.023	0.91 ± 0.05	0.90 ± 0.05	0.014	0.340
Systolic blood pressure (mm Hg)	124 ± 14	117 ± 15	0.001	126 ± 15	123 ± 14	0.094	0.038
Diastolic blood pressure (mm Hg)	81 ± 9	77 ± 11	0.005	83 ± 8	80 ± 9	0.047	0.108
Fasting plasma glucose (mmol/liter)	7.0 ± 0.8	5.6 ± 0.9	0.000	6.8 ± 0.9	6.4 ± 1.6	0.091	0.000

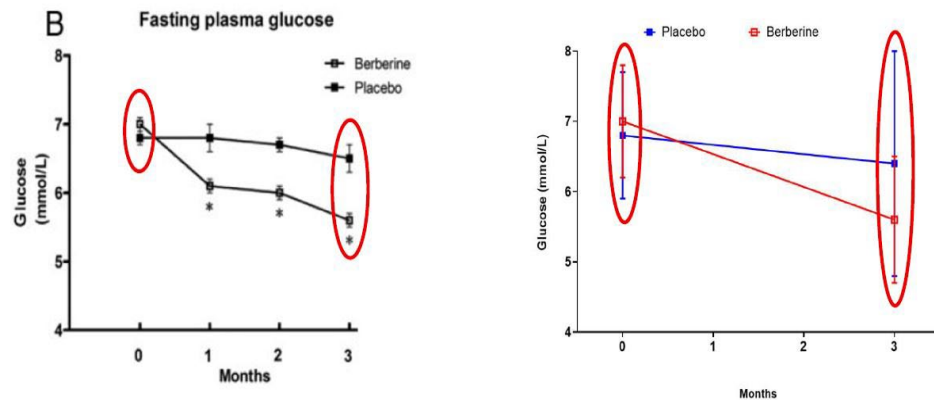
c. Exh. 1006, p. 4 (red box added), above.

d. While the one (1) and two (2) month data are not provided in Table 1 or elsewhere in the article, an accurate plot of the data for the zero (0) and three (3) month data from Table 1 appears as follows:



e.

f. This representation of the data (based on the numbers from Table 1) looks significantly and inexplicably different than what is represented in Zhang:



g.

FIG. 3. Body weight (A), fasting plasma glucose concentrations (B), serum triglyceride concentrations (C), serum cholesterol concentrations (D), and serum LDL-c concentrations (E) during treatment of berberine (□) and placebo (■). Data displayed as means $\pm$ se. *, $P < 0.0001$ after 1, 2, or 3 months treatment vs. before treatment within each group.

153. Therefore, based on this data representation irregularity, there is reason to be highly skeptical of the claim for Fig. 3B that the statistical significance is at the $p < .0001$. Thus, the veracity of the data in Zhang is highly questionable at best, and I believe that a POSITA would be highly skeptical of everything in Zhang once this questionable representation of data and statistical significance related to Fig. 3B were realized, which for a POSITA would be quick.

154. Petitioner and Shebuski rely on Zhang to support the obviousness contentions in Ground 3, to try to satisfy the limitations of claims 1 and 2 of the '961 Patent and to provide a viable reason to combine Zhang with Feng with a reasonable expectation of success. *See* Petition (Paper 2), at pp. 49-56; Exh. 1003, at ¶¶ 74-77, 80-82, 88-93. Based on the foregoing irregularities with the data in Zhang, a POSITA would not have relied on Zhang at all.

155. In ¶ 53, Shebuski presents a fourth ground where it is purported that “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.” *See* Exh. 1003, at ¶ 53.

156. In ¶ 54 of the Shebuski report contends that there is a reasonable expectation of success of using the BSA conversion by corroboration with FDA

guidance. For reasons already stated, and elsewhere, I do not believe this to be a valid expectation.

157. In ¶ 55, Shebuski continues discussions of the FDA guidance. Again, for reasons already stated, this does not appear to be compelling.

158. In ¶ 56, Shebuski further continues discussions of the FDA guidance. Again, for reasons already stated, this does not appear to be compelling.

159. In ¶ 57, Shebuski continues further discussions of the FDA guidance. Again, for reasons already stated, this does not appear to be compelling. To expand further, the presented postulation of the applicability of the BSA calculations has already been addressed and rejected as to what a POSITA would accept as prior art. For this discussion kindly refer to the sections presented in the instant report referring to the objections presented by Blanchard, and Frazier and Price. As such, there has not been presented a convincing argument that claims 1, 2, 5, 6 and 7 would have been obvious to a person of ordinary skill in the art from the combined teachings of Turner and Shaw.

2. Claim 2 - The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels

160. The Claim 2 discussion is introduced at ¶ 58 on pg. 30 of Shebuski.

161. Claim 2 is a dependent claim, i.e., dependent upon claim 1. I am not a legal expert, but it is my understanding that, as a dependent claim it automatically

includes all the limitations of the claim it references, that is, in this case, Claim 1, while narrowing the invention by adding the specific features or components presented in Claim 2.

162. Claim 1 has already been addressed and the so-called prior art presented by Shebuski found to be lacking, that is, the prior art presented by Shebuski, and related arguments, have been insufficiently compelling to make Claim 1 of the '961 invention obvious to a person having "ordinary skill in the art."

163. Shebuski's position on Claim 2 is summarized in ¶ 58 (Exh. 1003, at ¶ 58. p. 30) as follows:

164. "For reasons I provide above, a POSA would understand that claim 2 would be satisfied if a prior art reference (or a combination of prior art references) demonstrates **via a glucose tolerance test that the administration of dihydroberberine would keep blood glucose levels closer to fasting blood glucose levels than berberine would.**" (emphasis added)

165. I respectfully do not agree with Shebuski's contention that claim 2 would be satisfied for the reasons he gave, here or elsewhere. That is, I respectfully disagree that a POSA would understand that claim 2 would be satisfied if a prior art reference (or a combination of prior art references) demonstrates via a glucose tolerance test that the administration of dihydroberberine would keep blood glucose levels closer to fasting blood glucose levels than berberine would."

166. In ¶ 59 Shebuski once again contends Exh. 1004 Turner satisfies as prior art, here by presenting “Turner demonstrates, via a glucose tolerance test, that administration of dihydroberberine would keep mice’s blood glucose levels closer to fasting blood glucose levels than berberine,” and presents Figs 3(B) and 3(C) from Turner in support of this contention. However, I must stress once again my disagreement with Shebuski’s reliance on Turner because the experiments as a whole run by Turner, were so substantially different from experiments referenced in the ‘961 patent, such that they are not measuring the result of the same phenomenon and thus cannot be presented as being comparable. There are not comparable as I have already pointed out in my report for at least one or more of the following reasons:

- a. Turner employed rodent models (mice and rats) whereas the ‘961 patent tested administration to humans.
- b. The Turner subjects were pre-fed a high fat diet for many days prior to the tests whereas the ‘961 patent tested administration to humans who experienced no pre-feeding.
- c. The Turner subjects (rodents) were pre-fed a BBR or dhBBR along with the pre-fed high fat diet for many days prior to the tests whereas the ‘961 patent tested administration of BBR or dhBBR to subjects (humans) who experienced no BBR or

dhBBR pre-feeding.

- d. The studies on subcellular organelles (mitochondria) run by Turner were not validated as predictive of human physiological responses.
- e. The pharmaceutically effective amount of dihydroberberine used with the rodents could not be predictive of the pharmaceutically effective amount of dihydroberberine administered to the humans, as already described.

167. Thus, a POSITA would conclude that the Turner glucose tolerance studies AS A WHOLE are so different from the glucose tolerance test used, but not claimed, in the '961 patent, namely: Claim 2 "the method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels" that the Turner studies are not relevant prior art as to Claim 2 of the '961 patent.

168. Furthermore, even if it were a viable comparison, which it is not, for the actual glucose tolerance test itself, Turner used an intraperitoneal system ("FIG 3... B: Glucose levels [measured] during an intraperitoneal glucose tolerance test (2 g/kg)" Turner, p. 1417, Exh. 1004 p. 4), or gavage method ("Pharmacokinetic analysis. Rats were fasted (12 h) and gavaged with 20 mg/kg BBR or dhBBR, and blood samples were obtained over the subsequent 24 h." Turner, p. 1415, Exh. 1004 p. 2) for their rodents whereas the '961 patent employed the standard test on humans

with no intraperitoneal system or gavage method for feeding pre-feeding. And, once again, the pre-feeding of the rodents over many days prior to the glucose tolerance test is quite dissimilar to the human tests in the '961 patent.

169. I respectfully submit that these differences illustrate the most obvious fallacy of this position taken by Shebuski, that is, that Shebuski presents an “apples and oranges” comparison of the results of the Turner rodent glucose tolerance tests to the glucose tolerance test used in the '961 patent examples. The Turner tests were performed in conjunction with prior administration of berberine or dihydroberberine along with HFD over many days and should not be compared to results of a glucose tolerance test performed immediately after administration of dihydroberberine or berberine, plus the other differences outlined above.

170. There is no element, or comparative element, in Claim 2, nor in any of the claims found in the '961 patent, that present such a requirement as is presented in the first line of Shebuski ¶ 59, that is, there is no requirement as “Turner demonstrates” that “via a glucose tolerance test, that administration of dihydroberberine would keep mice’s blood glucose levels closer to fasting blood glucose levels than berberine.” *See* Exh. 1003, at ¶ 59. Thus, Shebuski’s assertion does even not address the claim limitations of claim 2 and provides little, if any, support for the conclusion that the challenged claims would have been obvious to a POSITA.

171. In ¶ 60 Shebuski continues his contention, presenting the area under the curve in Fig. 3(C). This does not overcome the arguments and shortcomings of the position as presented above. Accordingly, Dr. Shebuski's reliance on this information does not address a limitation of claim 2 and does not advance the contention that the challenged claims of the '961 patent would have been obvious to a POSITA.

172. In ¶ 61 Shebuski reiterates his contention that “a POSA [POSITA] 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...” Once again this does not add any new argument and does not meet the limitations of Claim 2, is similarly immaterial to the '961 patent, does not demonstrate that the challenged claims of the '961 Patent would have been obvious to a POSITA.

173. From the above, one can only respectfully conclude that this is a series of straw-man arguments, with no basis in the patent, and thus does not meet the limitations of Claim 2.

3. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

174. In ¶ 62 Shebuski addresses Claim 5 of the '961 patent. Here, he presents a quote from Turner that BBR is “administered orally” as follows: “(“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.”).

175. But Shebuski leaves out an important factor. Simply stated, the oral administration of **berberine (BBR)** is not oral administration of **dihydroberberine (dhBBR)**.

176. Furthermore, administering a nonprescription drug orally can take many forms. Turner does not specifically state that dhBBR is “used as a... oral drug” or that this means it is administered as a capsule or tablet. Many oral Chinese medications are administered as liquids and the administration of liquids do not teach the oral administration of a capsule or tablet. The oral administration of liquids is not being claimed in Claim 5 of the ‘961 patent. Thus, the quote is insufficiently compelling to teach Claim 5 of the ‘961 patent which requires dihydroberberine be orally administered as a capsule or table.

177. Furthermore, Turner did not employ, or state that he employed a capsule or a tablet, but referred to others in China and only stated that it was an oral drug, not formed into a capsule or tablet.

178. Furthermore, the administration of BBR in China was referred to by Turner as “commonly used as a nonprescription oral drug in China to treat gut infections and diarrhea with few side effects,

179. “Oral” administration may also include liquid formulations, or powders, thus the reference that Chinese “administered” is only in the Turner reference to references is presented without differentiation as to form, does not specify form, and thus, in the view of a POSITA, is not obvious and does not satisfy Claim 5 of the ‘961 patent.

180. In ¶ 63 Shebuski states that dhBBR was provided in the HFD, but this is not a tablet or oral administration. Furthermore, Turner did not administer either BBR nor dhBBR orally as a capsule or tablet, but only as a component of diet fed over a two-week period as part of a high-fat diet.

181. Also, in ¶ 63 Shebuski states dihydroberberine can be... “kept in a dry and solid form.” But, concerning the dhBBR, no shelf life, or stability over time, or time span of storage, or degree of dryness, or moisture effect on stability, or storage conditions, of stability when mixed with other materials, or stability with rodent chow, or how it should be mixed with rodent chow (As a powder? As a liquid? As chunks?) and effects of chemical interactions once combined) are mentioned or implied. Thus, Turner does not imply that dhBBR can be sufficiently stable to be vended in a tablet or capsule form. Thus, “kept in a dry and solid form.” would not persuade a POSITA that claim 5 is satisfied.

182. In ¶ 64 Shebuski presents the concept that “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.” But, based upon Turner, this would mean that dhBBR should be mixed into a high fat diet and in that way administered to humans over a period of a number of weeks as was done with Turner’s rodents. In the extreme patients would be required to consume the dhBBR as part of a standard rodent diet, if such a “customary approach” were to be followed exactly. The ‘961 patent makes no such claims of feeding humans high fat rodent (or human) diets laced with dhBBR, or to any aspect of this. Thus, a POSITA would not be persuaded that this ‘customary’ procedure is satisfied by Turner and thus would not be persuaded that this element of claim 5 is satisfied by Turner. Shebuski further invokes Zhang, Exh. 1006, but Zhang only administered BBR, not dhBBR (see Zhang “Treatment” section). And Shebuski then further invokes Liu, (See Exh. 1010), but Liu only states the subjects were orally dosed or administered, with no mention of tablets or capsules or powders or liquids or rat chow. Thus, once again, these publications would not constitute prior art and thus would not be persuasive to a POSITA that they satisfied this element of claim 5.

4. Claim 6 - The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

183. In ¶65 Shebuski effectively repeats the arguments he presented in his ¶
64. Once again that information and publications would not constitute viable prior

art and thus would not be persuasive to a POSITA that they satisfied this limitation of claim 6.

184. Noting the wording of Claim 6, that “the dihydroberberine is orally administered as at least one of a food product or beverage product,” one can readily ascertain that that stands in contrast to pre-feeding, and pre-feeding a high fat diet and the like, or pre-feeding over many days, or any other variation of the Turner procedures, as is exemplified by Turner “Research Design and Methods” section as follows: “Animals were randomly assigned to receive either standard control rodent diet or a high-fat diet (HFD) to generate insulin resistance (9,10). 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 $100 \text{ mg} \cdot \text{kg}^{-1} \cdot \text{day}^{-1}$ for the final 2 weeks of feeding.”

185. A POSITA would immediately recognize that Turner’s administration or pre-feeding of food laced with dihydroberberine as described above is quite different from, and does not teach, the fashion in which dihydroberberine is “orally administered as at least one of a food product or beverage product” as described in Claim 6 of the ‘961 patent, and thus recognize that it should not be considered as prior art.

186. Furthermore, the feeding aspects of Turner were distinctly different from the administration of food and medication as that was presented in the examples

given in the '961 patent. As previously mentioned, on comparison to the studies presented in Turner, the examples presented in the '961 patent (Col. 9:08-67) demonstrating the action of dihydroberberine...

- a. Were not run on rodents (mice or rats), or other non-human animals,
- b. Were run on humans,
- c. Did not involve the use of a hyperinsulinemic-euglycemic clamp,
- d. Did not involve gavage (force feeding of the subject by administering food and/or medication directly into the stomach using a small plastic or rubber tube) as a means of feeding glucose to a subject, or employed as a means for any feeding purposes (for example the Claim 6 dihydroberberine orally administered as at least one of a food product or beverage product), and not involved in, or for, any other purpose at all and is absent in the '961 claims as well.
- e. Were not performed using an **intraperitoneal** glucose tolerance test.

187. Thus, for this and other reasons presented, the rodent results from Turner cannot be used in a predictive capacity for human studies.

188. In ¶ 66 Shebuski reiterates his previously presented quote that

dihydroberberine can be... “synthesized and kept in a dry and solid form.” But, once again, no shelf life, or time span of storage, or degree of dryness, or storage conditions are mentioned or implied. Thus, Turner does not imply that dhBBR can be sufficiently stable to be vended in a tablet or capsule form. Thus, “kept in a dry and solid form...” would not persuade a POSITA that claim 6 is satisfied.

189. In ¶ 67 Shebuski opines that “Turner teaches that the dhBBR is administered orally to the mice because dhBBR is administered the same way BBR is administered in the high-fat-diet (HFD).”

190. In ¶ 68 Shebuski opines on the motivation underpinning his opinion. However, as previously stated, based upon Turner, this would mean that dhBBR should be mixed into a high fat diet and in that way administered to humans over a period of a number of weeks as was done with Turner’s rodents. In the extreme, patients would be required to consume the dhBBR as part of a standard rodent diet, if such a “customary approach” were to be followed exactly. The ‘961 patent makes no such claims of feeding humans high fat rodent diets laced with dhBBR, or to any aspect of this. Thus, a POSITA would not be persuaded that this ‘customary’ procedure is satisfied by Turner and thus would not be persuaded that claim 5 is satisfied.

5. Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily

191. In ¶ 69 Shebuski proposes that “Turner teaches that the dihydroberberine is administered daily on rodents.” But that is not exactly correct. Firstly, his contention that “Turner teaches that the dihydroberberine is administered daily on rodents” is not true. As already mentioned, Turner’s animals (rodents) were randomly assigned to receive either standard control rodent diet or a high-fat diet (HFD). It says nothing about their feeding regimen. Turner does not imply any feeding schedule. The animals may have been fed ad libitum, may have been fed twice a day, may have been fed every second day, or any other variation. No recording device was used by Turner to record rate of consumption of the diet that might support Shebuski’s contention. Next, the ‘961 patent clearly states “administered at least once daily.” *See* Exh. 1001, at claim 7. Thus, in comparison, Claim 7 of patent ‘961 clearly states a daily administration, independent of any other feeding regimen. Thus, a POSITA would not be persuaded that this feeding rate (once daily) procedure as presented in Claim 7 is satisfied by Turner who stated the rodents “received” various rodent diets and thus would not be persuaded that this frequency of drug administration element of claim 7 is satisfied.

192. In ¶ 70 Shebuski contends that “a POSA [POSITA] would have a reasonable expectation, based on preclinical animal studies, that administration of

dhBBR daily to humans would be a successful strategy for managing glucose tolerance.”For the reasons stated above I disagree with Shebuski’s contention. Thus, a POSITA would not be persuaded that this drug administration element of Claim 7 is satisfied by Turner .

193. For the reasons stated above I disagree with Shebuski’s conclusions in his ¶ 70 and, respectfully, I do not see that he presented a persuasive argument that POSA [POSITA] would have a reasonable reason to conclude that a daily administration of dhBBR is obvious.

B. GROUND 2: Claim 5 Is Not Obvious Over Turner in View of Shaw and Zhang

1. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

194. In ¶ 71 Shebuski initiates his contentions in GROUND 2, that Claim 5 is obvious over Turner in view of Shaw further in view of Zhang by once again presenting that “Turner teaches that BBR is administered orally.”

195. Note that Claim 5 is a dependent claim of Claim 1 and thus must include the elements and limitations of Claim 1.

196. As already stated, clearly Turner does not teach that BBR is administered orally *per se*, but rather admixed with standard rodent diet or high-fat rodent diet,

and Turner did not employ, or state that he employed, a capsule or a tablet either, but “provided” rodents BBR over an extended period of time as a component of their diet fed over a two-week period as part of a high-fat diet, and furthermore only referred to others in China and only stated that it was an oral drug, not formed into a capsule or tablet.

197. In ¶ 72 Shebuski again stated his believe that “Turner teaches that the dihydroberberine is administered orally because dhBBR is administered to the mice the same way BBR is administered in the high-fat-diet (HFD) diet.” But admixing dhBBR in a rodent diet is not the same as “The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet” as is recited in Claim 5, and more specifically “to an individual” (human) as recited in Claim 1. Also, Shebuski reiterates that dihydroberberine may be prepared as a filter cake that “was dried overnight” this says nothing about whether it was administered orally as a capsule or tablet.

198. In ¶ 73 Shebuski once again introduces Zhang and states that “Zhang teaches that BBR is administrated orally in tablet (a dry and solid form) to diabetic patients.” But, once again, no shelf life, or stability over time, or time span of storage, or degree of dryness, or moisture effect on stability, or storage conditions, of stability when mixed with other materials, or stability with rodent chow, or how it should be mixed with rodent chow (As a powder? As a liquid? As chunks?) and

effects of chemical interactions once combined) are mentioned or implied. Thus, Turner does not imply that dhBBR can be sufficiently stable to be vended in a tablet or capsule form. Furthermore, the '961 patent does not claim administration to diabetic patients but rather to individuals as "A method of managing glucose tolerance" ('961 Patent, Claim 1) Thus, "kept in a dry and solid form" as stated by Turner, even in light of Zhang, would not persuade a POSITA that elements of claim 5: "The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet" is satisfied.

C. GROUND 3: Claims 1, 2, 5, and 7 Are Not Obvious Over Zhang in View of Feng

1. Claim 1:

a. A method of managing glucose tolerance in an individual comprising

199. In ¶ 74, (In Section IX, The Challenged Claims of the '961 Patent, ¶74, p. 36 of the Shebuski declaration (Exh. 1003, p. 36)), Shebuski presents his position that Claims 1, 2, 5, 7 Are Obvious over Zhang in View of Feng and states that "Zhang teaches a method of managing glucose tolerance in humans because Zhang discloses treatment of diabetic patients."

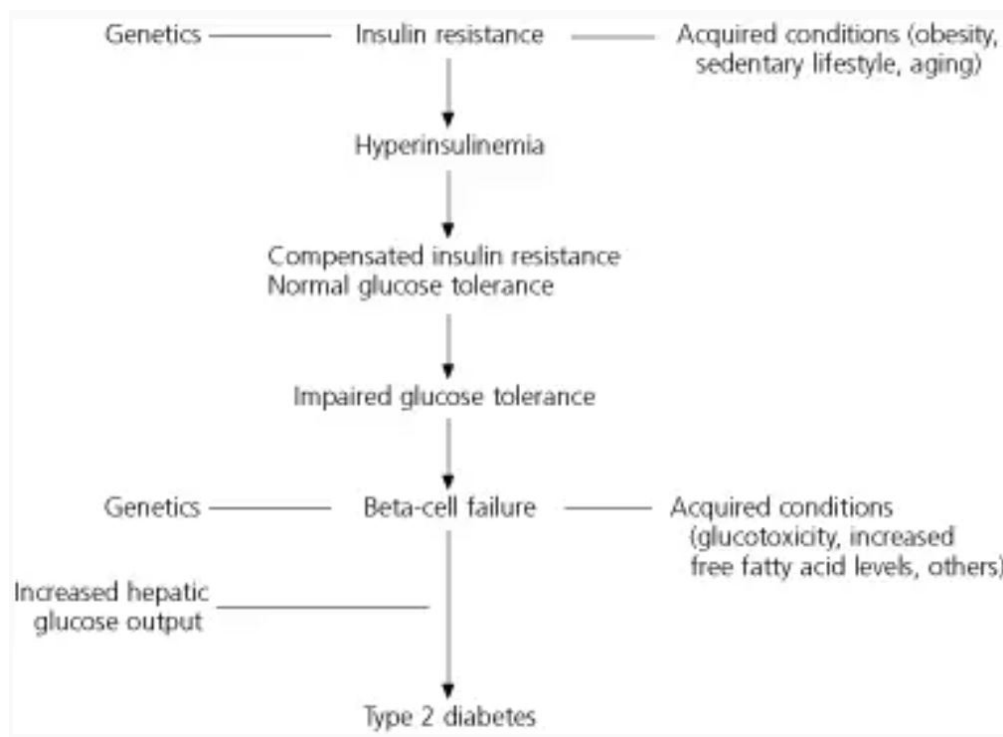
200. I disagree with this position. Claims 1, 2, 5, and 7 Are Not Obvious Over Zhang and/or in view of Feng for the reasons that follow.

201. Shebuski presents a position, drawn from the Claim 1 preamble, that “Zhang teaches a method of managing glucose tolerance in humans because Zhang discloses treatment of diabetic patients” and is thus prior art. This is so general that it is irrelevant. Zhang indeed presents a position that is related to diabetes treatment. But so have many dozens or hundreds of treatments reaching back into ancient times, which have had varying degrees of very modest success, until the introduction of insulin treatment.⁵ *See* Exh. 2161. Thus, respectfully, Shebuski’s contention has no genuine merit and Zhang is not applicable prior art relative to the ‘961 patent for these reasons, as well as those noted above.

202. As already stated in this report, glucose tolerance and diabetes are managed differently since they are distinctly different health situations and approaches to treatment are differently designed and separately considered. Managing glucose tolerance (which is what is presented as a limitation in Claim 1 and all claims dependent upon Claim 1, since, by definition under patent law, a dependent claim incorporates all the elements and limitations of the previous claim it refers to) is not the same thing as managing type 2 diabetes. Glucose tolerance is a physiological response that describes how well your body processes the simple

⁵ Exh. 2161 – Bliss, M. The discovery of Insulin, 25th anniversary, review by Clarfield, A. M., JAMA, Vol 301, No. 15 April 15, 2009.

sugar, glucose (dextrose), including fasting levels of glucose, and the glucose tolerance test is a diagnostic tool to measure if the processing is normal (≤ 139 mg/dL after 2 hours) or impaired (140 to 199 mg/dL after 2 hours). If impaired, the condition is referred to as prediabetes, a risk factor, but not diabetes. In contrast, as explained in Nathan (Exh. 2158), type 2 diabetes is the actual clinical diagnosis where the blood sugar levels are chronically at a high level due to the inability to properly use or make insulin, at a higher glucose level than the others (level chronically ≥ 200 mg/dL). *See* Exh. 2158, pp. 1-7. The differentiation is diagrammed in Rao and clearly shows the differences; figure 1 from Rao, Etiologic sequence for the development of type 2 diabetes, shown next. *See* Exh. 2159, p. 3.



203.

204. Shebuski ¶ 74 presents Zhang, where Shebuski contends that “Zhang

teaches a method of managing glucose tolerance in humans because Zhang discloses treatment of diabetic patients.” *See* Exh. 1003, at ¶ 74. However, Zhang is not relevant since no claims in the ‘961 patent specifically address diabetes and no diabetes treatment method is claimed.

b. administering a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine

205. Shebuski ¶¶ 75-77 similarly presents various aspects of Zhang that disclose the administration of BBR to patients (an individual) for diabetes treatment and or improvement in glucose tolerance. *See* Exh. 1003, at ¶¶ 75-77. But BBR is berberine. Unlike the ‘961 patent, Zhang does not address the administration of dihydroberberine but only the administration of berberine. This is clearly presented in the Zhang publication: “Conclusions: Berberine is effective and safe in the treatment of type 2 diabetes and dyslipidemia.” *See* Exh. 1006, at p. 1. In contrast to Zhang, the ‘961 patent does not involve the administration of berberine for diabetes treatment and / or improvement in glucose tolerance. Rather, the ‘961 patent involves the administration of dihydroberberine for managing glucose tolerance and Claim 1, as well as claims 2, 5, 6, and 7, and the ‘961 patent involves administration

of a pharmaceutically effective amount of dihydroberberine, not berberine

206. At no point does the ‘961 patent claim the administration of berberine itself but rather “one or more berberine metabolites (e.g., dihydroberberine and/or tetrahydroberberine).”

207. Thus, Shebuski’s position that Zhang presents applicable prior art has no genuine merit.

208. In ¶ 77 Shebuski presents the levels of BBR administered to type 2 diabetic patients by Zhang. This is not relevant and thus is not prior art since Zhang administers BBR while the ‘961 patent involves the administration of dhBBR and BBR metabolites, but not BBR. Furthermore, Zhang is treating diabetes whereas the ‘961 patent involves a “method of managing glucose tolerance.”

209. Shebuski introduces Feng as a prior art reference. *See* Exh. 1003, at ¶¶ 78-79. Here, Shebuski presents the basis for this purported prior art contention as follows:

210. “Feng concludes that “dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption.” Exh. 1007, at 8. To reach this conclusion, Feng teaches that dhBBR was identified as a metabolite in the intestines of rodents fed BBR in their chow diet. *Id.* at Fig. 1(C).”

211. However, administration of dhBBR to a subject to manage glucose tolerance is the basis for the invention described in the ‘961 patent. In contrast to

this, Feng presents research that describes the intestinal microbial conversion of BBR to dhBBR, and a subsequent conversion of dhBBR to BBR. This is totally different from the invention described in the '961 patent, where BBR is never administered at any point. In effect Feng is presenting *in situ* microbial synthesis of dhBBR from BBR, which is totally irrelevant to the '961 patent since BBR is never administered to individuals/patients in the '961 patent and no microbial conversions are claimed, *in situ* or *in vitro* or elsewhere. Thus, Feng does not teach any elements that should be considered as prior art relative to the '961 patent.

212. In ¶ 79, Shebuski presents the observation from Feng “that the bacterial from the guts [rodent intestines] converted BBR to dhBBR.” That is all well and good. But the '961 patent involves the administration of dhBBR (and dhBBR metabolites) and not BBR. Therefore, this observation is irrelevant. Thus, despite this observation, Feng does not teach prior art relative to the '961 patent.

213. Furthermore, in ¶¶ 79-80, Shebuski presents Feng’s “transient form” concept as prior art. However, neither Shebuski nor Feng seem to understand what a biochemical “transient form” is. In biochemical (enzymatically-catalyzed) reactions a transient form is short-lived (fractions of a second and sometimes even as short as microseconds) intermediate form (in, what is often called, the transition state) of a chemical. *See* Exh. 2162, p. 7; Exh. 2163, p. 74 (book page). The transient form stays bound to the enzyme as part of a transient molecular assembly. This

transient form is part of a complex that is not a stable product. That is, the "transient form" refers to the highly reactive, temporary state of a substrate bound to the enzyme's active site. Often called a reaction intermediate or transition state, it is the short-lived, transient part of the transformation of the starting material (known as a substrate), with a reaction that goes from substrate through an intermediate, bound, transient form (effectively, the enzyme-substrate complex) that is eventually converted to the product and released as the product of the reaction. The transient form is not released from the enzyme under normal conditions. Thus, Shebuski's contention that relies upon the production of a "transient form," and nominates dhBBR as the "transient form" falls apart. The appropriate conclusion here is that Shebuski's contention that Feng is prior art to the '961 patent has no merit and Feng does not teach prior art relative to the '961 patent.

214. By the same logic, in other locations in the Shebuski report (Exh. 1003), where conclusions (including conclusions of purported prior art) are presented, that are dependent upon the faulty use of the term "transient form," those conclusions are also discredited, i.e., the already referenced ¶¶ 79-80, plus ¶¶ 87, 92, 93, 96, 98, 99 [Exh. 1003, p. 43-44, 46, 47 and 48]. Thus, at no point is Feng applicable prior art relative to the '961 patent.

215. In light of the above, the rate of absorption of BBR in the intestines is likewise not relevant.

216. In ¶ 80, Shebuski discusses Zhang in view of Feng and also attempts to present dhBBR as a “pro-drug” as part of his incorrect “transient form” position, since it is converted at some point the organism intestines, or in the blood, to BBR. This is only incidental to the administration of dhBBR claimed in the ‘961 patent. Metabolic or abiotic alteration of the dhBBR does not change the fact that what is administered is dhBBR and not BBR. Thus, once again, Feng (which does not mention the term “prodrug” or “pro-drug”) does not teach applicable prior art relative to the ‘961 patent.

217. However, even if it is deemed that the criticism of the use of the term “transient form” is inappropriate, other arguments, such as the fact that the ‘961 patent does not claim the administration of berberine to subjects, with or without microbial transformation, are sufficient to reject the use of Feng as prior art.

218. In ¶ 81, Shebuski presents the observation that “Feng further discloses that dhBBR “has an intestinal absorption rate 5-fold that of BBR in animals.”” Exh. 1003 at ¶ 81.

219. This observation is not a compelling predictor of appropriate human dosage since it does not take into account the subject individual’s already-described pharmacokinetic factors, including individual and species factors such as absorption rate (including malabsorption rates due to such conditions as disease states), distribution in plasma and tissues (including binding to proteins such as albumin),

excretion (clearance by all eliminating organs), and metabolism (including cytochrome P450 and cytochrome P450 reductase) as described in Frazier and Price (*see* Exh. 2160) and elsewhere.

220. Clearly these are sufficient to reject the use of Feng or Zhang in View of Feng to claim obviousness of claims 1, 2, 5, 7.

c. A POSITA Would Not Have Been Motivated to Modify Zhang Based on Feng with a Reasonable Expectation of Success

221. Again, it is my understanding that the motivation to combine element of the obviousness analysis is separate and distinct from the reasonable expectation of success element. Dr. Shebuski appears to have conflated them, which, I understand is incorrect.

222. That said, for the reasons already set forth above, as well as the following, I disagree with Dr. Shebuski's analysis.

223. In ¶ 82 Shebuski presents his "first" part of the discussion in this section by stating that "Zhang discloses clinical studies demonstrating that BBR is effective in managing glucose tolerance of humans." This argument is flawed for a number of reasons, especially since the '961 patent does not claim BBR as a treatment for managing glucose tolerance in humans and furthermore does not propose to use berberine "in the treatment of diabetes and dyslipidemia."

224. In ¶ 83 Shebuski presents his "second" part of the discussion in this

section by presenting the problem of bioavailability of BBR and Feng's position that "BBR is also "very difficult for intestinal epithelial to absorb," and Turner's observation of "A potential disadvantage of BBR... for treatment of diabetes... [requiring] the need for relatively high doses in rodents to achieve beneficial metabolic effects." Again, the '961 patent does not claim the use of BBR, nor the treatment of diabetes and thus, even with a combination including Feng, the elements of the '961 patent are not met.

225. In ¶ 84 Shebuski presents his "third" part of the discussion in this section by presenting his contention that "a POSA [POSITA] understood that dhBBR is a known BBR derivative with improved absorption characteristics," and defended this by presenting Turner's unproven hypothesis that "dhBBR was predicted to have improved absorption characteristics based on a structural analysis of the molecules." Besides presenting an unproven hypothesis, the additional shortcomings in this logic is that the Shebuski report presented no literature that had been published prior to the priority date that revealed if administration of dhBBR to humans at the claimed dosages would be successful. "Predicting," especially predicting absent validation, is not demonstrating or discovering.

226. In ¶ 85 Shebuski's presentation of predictions and rodent studies and intestinal microbial transformations still do not stand as prior art to overcome the objections already presented in the current report,

227. In ¶ 86 Shebuski further recapitulates the above-discussed absorption characteristics and Feng's microbial conversion results "where BBR was incubated with bacteria isolated from rodent and human intestines." But the '961 patent does not rely upon microbial transformations of BBR to dhBBR in the intestines (only dhBBR is administered as per Claim 1 of '961 patent), or Caco-2 cell line models for rates of absorption, or an understanding of unsupported theories of molecular structure configurations as reasons for absorption or any of the other predictions or observations presented by Shebuski. Thus, none of the presented materials constitutes relevant prior art in relation to the '961 patent.

228. In ¶ 87 Shebuski presents his "fourth" part of the discussion in this section by presenting Feng's studies he contends supports his position that "a POSA will have a reasonable expectation of success that dhBBR, as an alternative to BBR for managing blood glucose levels, including that managing blood glucose levels." However, Feng never states the use of "dhBBR, as an alternative to BBR for managing blood glucose levels." As a matter of fact, Feng never mentions "managing blood glucose levels" or "managing blood glucose" or "managing glucose" or "managing" anything at all. I respectfully submit that Shebuski chose these terms since they echo Claim 1 of the '961 patent "A method of managing glucose tolerance..." even though these terms are not presented by Feng.

229. In ¶ 88 Shebuski theorizes that "A POSA would have a reasonable

expectation of success that dhBBR can be administered at a dosage that is at least five-fold lower.” I addressed the deficiency of this argument about absorption rate extrapolation between rodents and humans above, and in addition, his theory is not supported by studies to render Claim 1 of the ‘961 patent obvious.

230. In ¶ 89 Shebuski further theorizes that Feng’s in vivo animal studies present a corroboration of a reasonable expectation of success but does not demonstrate validation as to why the presented oral studies, with massive error bars (with only upper halves shown), support this theory.

231. In ¶ 90 Shebuski presents Feng permeability coefficient information, but does not demonstrate how this pertains as Claim 1 prior art, especially since it is a theoretical connection as evidenced by the comment: “Regardless of whether the Papp(AP-BL) coefficient accurately reflects how a human’s dhBBR intestinal absorption rate compares with the BBR absorption rate...”

2. Claim 2 - The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels

232. In ¶ 91 Shebuski presents his contention relating to Claim 2 that “Zhang teaches that administration of BBR reduces fasting glucose levels.” Shebuski continued... “As compared with subjects who received placebo, those receiving berberine had a significant improvement in fasting plasma glucose ...”). For this observation, Zhang did not administer dihydroberberine but rather administered

berberine and furthermore did not reveal the quantitative meaning of what constituted “significant,” i.e., did not reveal how much of a change would be considered significant. Thus, for these reasons alone Zhang should not be considered as being relevant prior art to the ‘961 patent.

233. In ¶¶ 92 and 93 Shebuski expands upon his position by presenting Feng’s purported teachings. Here Shebuski contends that “Feng discloses that “dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption.” Once again, as previously stated, it must be pointed out that administration of dhBBR to a subject is the basis for the invention described in the ‘961 patent. In contrast to this, Feng presents research that describes the intestinal microbial conversion of BBR to dhBBR, and a subsequent conversion of dhBBR to BBR. This is totally different from the invention described in the ‘961 patent, where BBR is never administered at any point. In effect Feng is presenting *in situ* microbial synthesis of dhBBR from BBR, which is totally irrelevant to the ‘961 patent since BBR is never administered to individuals / patients in the ‘961 patent and no microbial conversions are claimed, *in situ* or *in vitro* or elsewhere. Thus, Feng does not teach any elements that should be considered as prior art relative to the ‘961 patent.

234. Furthermore, as previously stated, Feng incorrectly uses the term “transient,” here in ¶¶ 92 and 93, and elsewhere. It must respectfully be reiterated

that neither Shebuski nor Feng seem to understand what a biochemical “transient form” is. In biochemical (enzymatically-catalyzed) reactions a transient form is short-lived (fractions of a second and sometimes even as short as microseconds) intermediate form (in what is often called, the transition state) of a chemical. *See* Exh. 2162, p. 7; Exh. 2163, p. 74 (book page). The transient form stays bound to the enzyme as part of a transient molecular assembly. This transient form is part of a complex that is not a stable product. It is the short-lived, transient part of the transformation of the starting material (known as a substrate), with a reaction that goes from substrate through an intermediate, bound, transient form (effectively, the enzyme-substrate complex) that is eventually converted to the product and released as the product of the reaction. The transient form is not released from the enzyme under normal conditions. Thus, Shebuski’s contention that relies upon the production of a “transient form,” and nominates dhBBR as the “transient form” falls apart. The appropriate conclusion here is that Shebuski’s contention that Feng is applicable prior art to the ‘961 patent has no merit.

235. Furthermore, in ¶¶ 93 Shebuski contends that “Zhang in view of Feng teaches that administering dhBBR will reduce fasting blood glucose levels because dhBBR gets rapidly converted back to BBR after absorption in intestine tissues and then enters the blood.” However, no such teaching or requirements or elements are present in the ‘961 patent in general and, more specifically in dependent Claim 2.

The purported conversion, first a microbial conversion of a fraction of BBR to dhBBR and then the purported mechanism that dhBBR gets rapidly converted back to BBR during or after absorption in intestine tissues and then enters the blood is not a required element of claim 2, which is just “The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels,” with no mechanistic requirements or knowledge of the conversion mechanism. Thus, Feng is irrelevant and neither Zhang alone nor Zhang in view of Feng, would have provided a POSITA with a motivation to modify Zhang or combine it with Feng with a reasonable expectation of success. Moreover, the combination of Zhang and Feng does not teach all of the limitations of Claim 2 of the ’961 patent and does not make Claim 2 of the ’961 patent obvious.

236. Addressing the motivation described in Shebuski ¶ 94, I disagree and believe that neither Zhang or Zhang in view of Feng, irrespective of the pharmacokinetic (*sic*, pharmacokinetic) data of Turner, do not motivate a POSA (POSITA) to modify Zhang with Feng with a reasonable expectation of success, and furthermore does not teach claim 2 of the ’961 patent, and thus is not prior art relevant to the claim, or any claim presented in the ’961 patent.

3. Claim 5 - The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet

237. In ¶¶ 95 Shebuski continues the contention that “A POSA Would Have

Been Motivated to Modify Zhang based on Feng with a Reasonable Expectation of Success” and here further contends that “Zhang teaches that the BBR is administered as tablets,” and defends this contention with “Exh. 1006, Zhang at 2560 (“Patients were randomized to receive berberine (0.5 g, twice daily) or placebo prepared in indistinguishable tablets.”).”

238. In ¶ 96 Shebuski further continues this contention and once again presents information concerning BBR (but not dhBBR) where “Feng teaches that BBR “ha[d] been used orally for decades in China as an over-the-counter (OTC) drug to treat diarrhea with good safety.” But no claims in the ‘961 patent, including Claim 5, claim diarrhea treatment.

239. And furthermore, ¶ 96 Shebuski continues and states that “dhBBR can be and was indeed administered orally to rodents to study its rate of absorption by the intestines. But the ‘961 patent does not involve, and does not claim, oral treatment of rodents, or to study its rate of absorption by the rodent intestines. And it does not appear that Feng orally administered dihydroberberine in capsule or tablet form to rodents. Thus, this reference to Feng is irrelevant to Claim 5 and, based upon this information, a POSITA would not have been motivated to modify Zhang based on Feng with a reasonable expectation of success.

240. In ¶ 97 Shebuski continues his contentions. Here he states that “Feng further teaches 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.”” Shebuski further supports this with “pharmokinetics” (*sic.* pharmacokinetics) observations from Turner relating to absorption in rat intestine tissues and blood. But the ‘961 patent does not involve, and does not claim, the administration of BBR to any organism, and does not claim a requirement that gut microbiota reduce BBR into its absorbable form of dhBBR or claim that dhBBR is oxidized back to BBR after absorption in intestine tissues and enters the blood.” Thus, these references to Feng and to Turner are irrelevant to Claim 5 and, even based upon this information, a POSITA would not have been motivated to modify Zhang based on Feng with a reasonable expectation of success.

241. In ¶ 98 Shebuski summarizes his position but does not add any additional information. Thus, my position is unchanged, that these references to Zhang and Feng and Turner, alone, or in various combinations, are not persuasive in presenting prior art that shows that Claim 5 would have been obvious to a POSITA, and, even based upon this information, a POSITA would not have been motivated to modify Zhang based on Feng and/or Turner with a reasonable expectation of success.

4. Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily

242. In ¶ 99 Shebuski addresses Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily. This is under the postulation

that A POSITA would have been motivated to modify Zhang based on Feng with a reasonable expectation of success. I disagree with this position as expanded upon below.

243. In ¶ 100 Shebuski presents a contention that “Feng discloses that “dhBBR is a transient form of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption.”” This has already been presented by Shebuski and has been rejected above by me on the basis of both bad terminology (the incorrect use of “transient form”) and the irrelevance of absorption characteristics and changes in BBR since dhBBR is administered as claimed in Claim 7, and not BBR, and the irrelevant of “administered at least once daily” as is part of the Claim 7.

244. A POSITA would not have been motivated to modify Zhang based on Feng and/or Turner with a reasonable expectation of success. Thus, these arguments do not present persuasive prior art relative to Claim 7 of the ‘961 patent, “Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily.”

245. In ¶ 101 Shebuski presents a contention that “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.” And that “this finding is corroborated by Turner.” Shebuski further presents the already

discussed absorption and conversion data of Turner.

246. In ¶ 102 Shebuski presents the contention that “Because BBR has already been administered orally at least once daily, and further because orally administered dhBBR would remain pharmacologically effective given BBR would 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. As explained above, a POSA would have been motivated to modify Zhang with Feng with a reasonable expectation of success.” There are no data that relates the BBR to dhBBR to the half-life of dhBBR in humans, and what concentration is required to achieve this, and what conditions alter this, making this contention irrelevant.

247. To summarize, each of these components are rejected for various reasons, alone or in combination. These include:

- a. Unlike Feng, which involves the administration of **BBR**, the ‘961 patent does not involve the administration of BBR.
- b. Unlike Zhang, which teaches that BBR is administered **twice daily** (not *at least* once daily as contended by Shebuski), Claim 7 teaches or claims “the method of claim 1 wherein the **dihydroberberine** is administered **at least once daily**.” Once daily and twice daily are very different things when it comes to such administrations.

- c. Feng discusses dhBBR formation in the intestinal lumen... and states dhBBR is a “transient form” of BBR in the intestinal lumen, with improved physiochemical characteristics for absorption whereas the ‘961 patent has no such claim, especially as part of Claim 7 of at least once daily administration.

248. Once again, a POSITA would not have been motivated to modify Zhang based on Feng and/or Turner, especially concerning rodent or microbiological studies, with a reasonable expectation of success relative to the administration of dihydroberberine “at least once daily.” Thus, the arguments presented by Shebuski do not present prior art relative to Claim 7 of the ‘961 patent, “Claim 7 - The method of claim 1 wherein the dihydroberberine is administered at least once daily.”

D. GROUND 4: Claim 6 Is Not Obvious Over Zhang in View of Feng Further in View of Turner

1. Claim 6 - The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product

249. In ¶ 103 Shebuski addresses GROUND 4: where he states that Claim 6 is obvious over Zhang in view of Feng further in view of Turner, here focusing on Claim 6 of the ‘961 patent, “The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.” Shebuski initiations his contention by repeating that “Turner teaches that dhBBR can be

synthesized and kept in a dry and solid form.”

250. As I have already stated in the current report Turner presents, concerning the dhBBR, no shelf life, or stability over time, or time span of storage, or degree of dryness, or moisture effect on stability, or storage conditions, of stability when mixed with other materials, or stability with rodent chow, or how it should be mixed with rodent chow (As a powder? As a liquid? As chunks?) and effects of chemical interactions once combined are mentioned or implied. Thus, Turner does not imply that dhBBR can be sufficiently stable or chemically (food) compatible to be orally administered as at least one of a food product or beverage product. Thus, “kept in a dry and solid form” would not persuade a POSITA that Claim 6 is satisfied, that is, a POSITA would not have been motivated to believe Claim 6 Is Obvious Over Zhang in View of Feng Further in View of Turner.

251. In ¶ 104 Shebuski contends that “Turner teaches that the dhBBR is administered orally to the mice because dhBBR is administered the same way BBR is administered in the high-fat-diet (HFD) diet,” and that BBR and dhBBR were provided in the HFD.

252. In ¶ 105 Shebuski presents his contention that “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. Exh. 1007, Feng at 5 (“dhBBR in its sulfate form (dihydroberberine sulfate) was previously reported

to exhibit better absorption in the intestine as compared with BBR.”)”

253. But, in contradiction to this, “better absorption” is never presented by the ‘961 patent, especially in conjunction with what I have already stated in the current report. (see ¶¶ 215, 218-219, 225, 227, 229, 231, 233, 239, 240, 243) In the Turner experiments **rodents** (not humans) were **pre-fed a HFD (high fat diet)**, whereas **there is no pre-feeding of subjects (humans) presented in the ‘961 patent**. That is, at no point does the ‘961 patent indicate or suggest the test subject was subjected to a **pre-fed, high fat diet (HFD)** (emphasis added).

254. Thus, different procedures for administration of the test compound(s) were followed, adding distance between the various studies.

255. One may conclude that, due to these important differences, Shebuski’s contention that, “in other words, Turner teaches that dhBBR is orally administered to the mice “as at least one of a food product”” is not valid.

256. Finally, in ¶ 106 Shebuski presents his contention that “A POSA would have been further 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.”

257. None of these items, alone or in combination would persuade a POSITA

that Claim 6 is satisfied, that is, a POSITA would not have been motivated to believe Claim 6 is obvious over Zhang in view of Feng further in view of Turner.

258. Once again, a POSITA would not have been motivated to modify Zhang based on Feng and/or Turner, especially concerning rodent or microbiological studies, with a reasonable expectation of success relative to “wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.” Thus, the arguments presented by Shebuski do not present prior art relative to Claim 6 of the ‘961 patent, “Claim 6 - The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.”

259. However, for the reasons already mentioned, none of these items, alone or in combination, would persuade a POSITA that Claim 6 is satisfied, that is, a POSITA would not have been motivated to believe Claim 6 is obvious over Zhang in view of Feng further in view of Turner.

X. RIGHT TO SUPPLEMENT

260. I reserve the right to supplement my opinions in the future to respond to any arguments that Petitioner raises. This declaration represents only those opinions that I have formed to date. I reserve the right to revise, supplement, and/or amend my opinions stated herein based on new information that becomes available to me and on my continuing analysis of the materials already provided. I may utilize the

documents cited and/or listed herein, or portions of those documents, as exhibits at any hearing or trial in this proceeding. I may further prepare and use exhibits that summarize portions of my testimony or key terms or concepts presented therein, or other demonstrative exhibits, at any hearing or trial in this proceeding.

261. I reserve the right to supplement my testimony and this report in response to any judicial determinations, in response to the arguments expressed by Petitioner or the opinions of Petitioner's experts in this proceeding, and/or in light of additional evidence or testimony brought forth at trial or otherwise brought to my attention after the date of my signature below.

XI. CONCLUSION

262. For the foregoing reasons, it is my opinion that the prior art does not teach the claim limitations of claims 1, 2, 5, 6, or 7 of the '961 patent alone or in combination, and that there are many reasons a POSITA would not have been motivated to combine or modify the prior art references relied upon by Petitioner, let alone with a reasonable expectation of success. On the contrary, the prior art teaches scientific uncertainty, mechanistic divergence, dosing ambiguity, and superior alternative compounds, all of which preclude a finding of obviousness.

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263. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Executed on: July 5, 2026



Dr. Louis DeFilippi,
President and Member,
Louis DeFilippi, LLC