

UNITED STATES PATENT AND TRADEMARK OFFICE
BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

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

U.S. Patent No. 10,278,961
Filing Date: April 19, 2017
Issue Date: May 7, 2019
Title: Administration of berberine metabolites
Inter Partes Review No.: IPR2025-01593

[EXHIBIT 1023]

**SUPPLEMENTAL DECLARATION OF DR. RONALD J. SHEBUSKI, SR.,
IN SUPPORT OF PETITIONER'S REPLY**

Table of Contents

I.	INTRODUCTION AND PURPOSE OF SUPPLEMENTAL DECLARATION	1
II.	ADDITIONAL MATERIALS REVIEWED	2
III.	RESPONSE TO PATENT OWNER'S ARGUMENTS	2
A.	Petitioner's Prima Facie Case of Obviousness Based on Grounds 1 & 2.....	2
B.	Petitioner's Prima Facie Case of Obviousness Based on Grounds 3 & 4.....	12
C.	Dr. Thomas Hartung.....	18
D.	Dr. Qiang Tong	19
E.	"5x More Available" Marketing Slogan	20
IV.	RIGHT TO SUPPLEMENT	24
V.	CONCLUSION.....	24

I, Ronald J. Shebuski, Sr., declare as follows:

I. INTRODUCTION AND PURPOSE OF SUPPLEMENTAL DECLARATION

111. I submitted a declaration in this proceeding on September 26, 2025, which was filed as Exhibit 1003 (“Original Declaration”) in support of the Petition for Inter Partes Review of U.S. Patent No. 10,278,961 (“the ’961 Patent”). I submit this supplemental declaration in support of Petitioner’s Reply to Patent Owner’s Response (Paper 18) to respond to the arguments raised in the Patent Owner Response and the accompanying rebuttal expert declarations of Dr. Thomas Hartung (Ex. 2107), Dr. Chad Kerksick (Ex. 2108), Dr. Qiang Tong (Ex. 2109), and Dr. DeFilippi (Ex. 2183).
112. I incorporate by reference my summary of background and qualifications (¶¶1–4), the terms of my compensation (¶5), and the relevant legal standards (¶¶7–15) set forth in my Original Declaration. My opinions here remain subject to the same standards, and nothing in this supplemental declaration is intended to withdraw or narrow any opinion expressed in my original declaration except as expressly noted below.
113. Unless otherwise indicated, I use the same defined terms, abbreviations, and exhibit numbering conventions used in my original declaration.

II. ADDITIONAL MATERIALS REVIEWED

114. In preparing this supplemental declaration, I have reviewed the Patent Owner's Response to Petition (Paper 18) ("POR"), Declaration of Dr. Thomas Hartung (Ex. 2107), Declaration of Dr. Chad Kerksick (Ex. 2108), Declaration of Dr. Qiang Tong (Ex. 2109), and Declaration of Dr. DeFilippi (Ex. 2183), and Declaration of Mr. Holzen (Ex. 2181). I have also reviewed relevant exhibits cited in the POR and expert declarations.

115. I have also reviewed additional exhibits below:

Nos.	Descriptions
1020	Sofianos Andrikopoulos et al., Evaluating the glucose tolerance test in mice, American Journal of Physiology-Endocrinology and Metabolism, (2008) E1323-1332.
1021	Ni Yanxia et al., Therapeutic effect of berberine on 60 patients with Type II diabetes mellitus and experimental research. CJIM (1988) (with English Abstract).
1022	Blog entitled "Glucovantage: Dihydroberberine for Superior Insulin Sensitivity," by Mike Roberto (January 15, 2020), available at https://blog.priceplow.com/supplement-ingredients/glucovantage .

III. RESPONSE TO PATENT OWNER'S ARGUMENTS

A. Petitioner's Prima Facie Case of Obviousness Based on Grounds 1 & 2

116. Based on my review of NNB's expert declarations, NNB's technical experts have not cited a single publication questioning Turner's conclusion

that dhBBR improves glucose tolerance. NNB's technical experts have not cited a single publication discouraging further diabetic research on dhBBR.

117. Turner teaches that dhBBR improves glucose tolerance through enhancing insulin activity for the whole body, not through drug mechanisms localized to the GI tract. Specifically, Turner teaches that BBR inhibits muscle mitochondrial respiratory complex I. Bonerge Ex. 1004 (Turner) at p. 1414. This mechanism allows BBR to activate AMP-activated protein kinase (AMPK). Bonerge Ex. 1004 (Turner) at p. 1414. AMPK is known to play a key role in regulating whole-body energy homeostasis; AMPK is an attractive drug target. Bonerge Ex. 1004 (Turner) at p. 1414.

118. Turner concludes that its findings indicate BBR is “likely the active moiety” of dhBBR, and that dhBBR is “in essence an effective vehicle for delivering BBR to the circulation.” Bonerge Ex. 1004 (Turner) at p. 1417. This indicates that dhBBR improves glucose tolerance through enhancing insulin activity for the whole body. Turner does not suggest or indicate that dhBBR improves glucose tolerance through mechanisms localized to the gastrointestinal tract.

119. Biguanides, more commonly known as metformin, is a diabetes drug. Metformin is known to exert its diabetic treatment effect at least in part by activating AMPK. Bonerge Ex. 1004 (Turner) at p. 1414.

120. The mechanism Turner teaches for BBR and dhBBR is the same mechanism by which diabetic drug metformin exerts its effects on humans, at least in part. Therefore, the results from an intraperitoneal test on diabetic mouse treated with dhBBR and the results from an oral test on diabetic patients treated with dhBBR likely will yield similar results. In other words, a POSITA would have reasonable expectations that Turner's IPGTT test establishing dhBBR's effect on glucose tolerance would translate successfully to human OGTT tests.
121. Based on my review of NNB's expert declarations, NNB's technical experts have not disputed Turner indicates that BBR improves glucose tolerance due to increased AMPK activity.
122. I understand some of the criticism against Turner originates from a publication by Andrikopoulos. For example, Dr. Kerksick cites Bowe to criticize the IPGTT test. NNB Ex. 2108 (Kerksick Decl.) at ¶¶45-48. Bowe is a review article. NNB Ex. 2094 (Bowe). Bowe's criticism of the IPGTT test cites the original research by Andrikopoulos et al.. NNB Ex. 2094 (Bowe) at pp. 003-004.
123. The version of the Andrikopoulos paper that NNB submitted appears to be a draft version of the Andrikopoulos. NNB Ex. 2154 (Andrikopoulos). I have reviewed the journal publication version of Andrikopoulos. Bonerge

Ex. 1020 (Andrikopoulos). The journal publication version includes typographical fixes such as fixing the mouse strain described in the draft version. See, e.g., NNB Ex. 2154 (Andrikopoulos) at p.16 (“C57BL/6” should have been “C57BL/6J”).

124. Andrikopoulos conducted his experiments on the same mouse strain that Turner used – male C57BL/6J mice. Bonerge Ex. 1020 (Andrikopoulos) at E1324. Andrikopoulos teaches that OGTT and IPGTT test results differ in terms of how high blood glucose levels peak and how long the peak sustains after the glucose load. Bonerge Ex. 1020 (Andrikopoulos) at E1326 and Fig. 3. Andrikopoulos teaches that “[t]he difference in glucose tolerance was greater following an OGTT (142%), in contrast to an IPGTT with a 127% difference between high-fat and chow.” Bonerge Ex. 1020 (Andrikopoulos) at Abstract. Andrikopoulos concludes that “the OGTT is a more sensitive technique to discern differences in plasma glucose and insulin levels in chow compared with high-fat fed C57BL/6J mice.” Bonerge Ex. 1020 (Andrikopoulos) at E1330.

125. Because Turner finds that dhBBR improves glucose tolerance under the less sensitive IPGTT test in the same HFD C57BL/6J mouse strain that Andrikopoulos studies, Andrikopoulos strengthens a POSITA’s expectation

that the Turner IPGTT test result establishing dhBBR's effect on glucose tolerance would translate successfully to human OGTT tests.

126. Because Turner indicates that dhBBR improves glucose tolerance due to increased AMPK activity (see above), and further because activating AMPK is a known mechanism for human diabetes drug (see above), a POSITA would have reasonable expectations that the Turner overnight GTT test result establishing dhBBR's effect on glucose tolerance would translate successfully to human OGTT tests.

127. Andrikopoulos teaches a GTT test under overnight fasting is not as sensitive as a GTT test following a six-hour fasting. Bonerge Ex. 1020 (Andrikopoulos) at E1328 and Fig. 1.

128. Because Turner finds that dhBBR improves glucose tolerance under the less sensitive GTT test under the overnight fasting protocol in the same HFD C57BL/6J mouse strain that Andrikopoulos studies, Andrikopoulos strengthens a POSITA's expectation that the Turner overnight fasting GTT test result establishing dhBBR's effect on glucose tolerance would translate successfully to human OGTT tests.

129. Turner's experimental protocol for the mouse GTT test is cross referenced to Molero at footnote 10. Bonerge Ex. 1004 (Turner) at p. 1415.

Molero's test protocol does not involve anesthesia. NNB Ex. 2105 (Molero) at 3412. The mouse blood samples were obtained from the tail tip of the mice. NNB Ex. 2105 (Molero) at 3412. This is typically done while the animal is awake.

130. Andrikopoulos has found that the use of anesthesia does not affect GTT test results if the experiments are properly controlled. Specifically, Andrikopoulos has found that "glucose intolerance was present whether the high-fat-fed mice compared with their chow-fed counterparts were anesthetized or conscious." Bonerge Ex. 1020 (Andrikopoulos) at E1330. Andrikopoulos concludes that glucose tolerance differences can be discerned "as long as the 'control' and 'test' mice are treated equally." Bonerge Ex. 1020 (Andrikopoulos) at E1330. Turner's experiments are properly controlled.

131. Based on my review of NNB's expert declarations, NNB's technical experts have not opined that a POSITA would suspect that a 486 mg/day dhBBR dosage would be pharmaceutically ineffective for managing glucose tolerance in humans.

132. I have studied a review paper by Blanchard et al. that is cited in Patent Owner Nanjing Nutrabuilding Bio-tech Co., Ltd.'s (NNB) Response to the Petition ("POR"). I understand that Blanchard criticizes Regan-Shaw and

stated his paper “aim[] to demonstrate why the recommendations presented by Regan-Shaw *et al.* are inappropriate.” NNB Ex. 2157 (Blanchard) at 1629. I also understand that the POR relies on Blanchard’s critique of Shaw to criticize the following statement from my Original Declaration explaining, among other, “Shaw discloses that the BSA normalization method is the ‘most appropriate’ method to translate drug dosage from animals to humans.” POR at ¶22.

133. Blanchard’s criticism of Shaw is driven by concerns over both under and overdosing. For example, Blanchard states that “[i]t is necessary for researchers working in translational medicine to recognize the fatal flaws of using BSA conversions to estimate PAD in humans, so that future human clinical trials do not yield spuriously negative findings based on major underestimations for therapeutic dose, or severe adverse events resulting from oversimplification of dose conversion.” NNB Ex. 2157 (Blanchard) at 1633. PAD is the acronym for pharmacologically active dose. NNB Ex. 2157 (Blanchard) at 1629.

134. A POSITA would have reasonable expectations that the 486 mg/day dhBBR dosage is effective in view of the state of diabetes research before April 2016.

135. Before 2016, a POSITA knew that 1,000 mg/day BBR would be effective for diabetes treatment. For example, Zhang teaches that BBR administered at 1,000 mg/day results in improved glucose tolerance test results as well as reduced fasting blood glucose levels. Bonerge Ex. 1006 (Zhang) at p. 2559 (abstract), 2561 (the primary outcomes).
136. Before 2016, a POSITA knew that dhBBR is more bioavailable, and orally ingested dhBBR would act as a vehicle for delivering BBR to the blood. For example, Turner teaches that 100 mg/kg/day dosage of dhBBR improves mouse's glucose tolerance while a dose of 560 mg/kg/day dose is needed for BBR. Bonerge Ex. 1004 (Turner) at pp. 1415-1416. Turner concludes that its findings indicate dhBBR is "in essence an effective vehicle for delivering BBR to the circulation." Bonerge Ex. 1004 (Turner) at p. 1417. As another example, Feng teaches dhBBR is more bioavailable. Bonerge Ex. 1007 (Feng) at p. 1. Feng further teaches that "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." Bonerge Ex. 1007 (Feng) at p. 1 (abstract).
137. A POSITA would have reasonable expectations that the 486 mg/day dhBBR dosage is unlikely to have severe adverse effects in view of the state of diabetes research before April 2016.

138. Before 2016, a POSITA knew that 1,500 mg/day BBR is safe.

Specifically, clinicians administered BBR to patients as high as 1,500

mg/day and reported that the dose is well tolerated by humans. Bonerge Ex.

1006 (Zhang) at p. 2560 (describing the state of the art).

“Several clinical investigations of berberine in the treatment of diabetes were reported in Chinese over the past 2 decades. Ni (4) reported that fasting plasma glucose concentrations in 60 patients with type 2 diabetes were reduced from 11.6 to 6.6 mmol/liter for 1–3 months when treated with berberine (0.3– 0.5 g, three times daily). Xie et al. (12) found that when berberine (0.3– 0.5 g, three times daily) was administered to 40 type 2 diabetic patients for 2 months without change in their previous therapy, fasting and postprandial plasma glucose concentrations were reduced by 21 and 27%, respectively. Wei et al. (13) also reported that treatment with berberine (0.5 g, three times daily) for 2 months in 30 type 2 diabetic patients with fatty liver decreased fasting plasma glucose, triglyceride, and total cholesterol concentrations by 31, 40, and 23%, respectively, and was associated with decrease in serum alanine aminotransferase and aspartate aminotransaminase concentrations. Participants in these clinical studies tolerated berberine well, with one subject in one study having mild gastrointestinal discomfort.

Bonerger Ex. 1006 (Zhang) at p. 2560. See also Bonerger Ex. 1021 (Ni) at

Abstract. A POSITA is unlikely to expect serious adverse effects for

patients taking 486 mg/day of dhBBR orally, which is about one third of the safe BBR dosage.

139. The FDA Guidance states “If the PAD is from an *in vivo* study, an HED can be derived from a PAD estimate by using a BSA-CF. This HED value should be compared directly to the MRSD.” Bonerge Ex. 1008 (FDA Guidance) at p. 12. “HED,” as used here, means “[a] dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose.” Bonerge Ex. 1008 (FDA Guidance) at p. 15. PAD, pharmacologically active dose, is the lowest dose tested in an animal species with the intended pharmacologic activity. Bonerge Ex. 1008 (FDA Guidance) at p. 15. BSA-CF is the acronym for Body surface area conversion factor. Bonerge Ex. 1008 (FDA Guidance) at p. 15. MRSD is acronym for maximum recommended starting dose. It means the highest dose recommended as the initial dose in a clinical trial. Bonerge Ex. 1008 (FDA Guidance) at p. 15. The FDA Guidance thus suggests that human equivalent dosage “can be derived from a PAD.” The suggestion to compare MRSD (“Maximum Recommended Starting Dose”) to HED, further implies HED is derivable from PAD and can be useful in drug development. Because Turner discloses dosages based on *in vivo* mouse studies, a POSITA would have reasonable expectations that the 486 mg/day HED dosage would provide the “same degree of effect” on humans.

140. The FDA Guidance teaches using BSA to derive the maximum recommended starting dose. Bonerge Ex. 1008 (FDA Guidance) at p. 1. Based on what FDA Guidance instructs, a POSITA conducting clinical diabetic research on dhBBR is likely to start from 48.6 mg/day after applying a default safety factor of 10. Bonerge Ex. 1008 (FDA Guidance) at pp. 9-10. If no efficacy is detected, the POSITA would escalate the dosage. A POSITA already knew that 1,000 mg/day BBR dosage would be clinically effective. See above. A POSITA also knew that dhBBR is more bioavailable. See above. Due to the state of the diabetic research on BBR and dhBBR, a POSITA therefore would have reasonable expectations that the lowest pharmacologically effective dhBBR dosage will be less than 800 mg.

B. Petitioner's Prima Facie Case of Obviousness Based on Grounds 3 & 4

141. I understand Patent Owner NNB argued 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.” POR at p. 42. I also understand that this criticism is directed at the “error bars” depicted Zhang’s Fig. 3B for allegedly not matching the data Zhang reported in Table 1. POR at pp. 39-42.

142. Zhang concludes that berberine taken at 1,000 mg/day is effective and safe in treating type 2 diabetes. Bonerge Ex. 1006 (Zhang) at p. 2559. Based on my review of NNB's expert declarations, NNB's technical experts have not cited a single publication questioning this conclusion.
143. I have reviewed the data reported in Table 1 and the error bars depicted in Fig. 3B. Zhang's data depiction in Fig. 3B based on Table 1 data is accurate.
144. A POSITA would understand Zhang's Table 1 data is in "mean $\pm$ SD" (standard deviation) format. This is evidence from the following explanation in Zhang: "Statistical analysis was performed using the SPSS 10.0 system (SPSS Inc., Chicago, IL), and data are presented as mean $\pm$ SD." Bonerge Ex. 1006 (Zhang) at p. 2561.
145. A POSITA would understand Zhang's Fig. 1 error bars is in " $\pm$ SE" (standard error) format based on the figure legend. Bonerge Ex. 1006 (Zhang) at Fig. 3 (legend).
146. $SE = SD/\sqrt{n}$. n is the sampling size.
147. As a POSITA would understand, standard deviation describes how spread out the individual data points are around the mean of the sample, and standard error measures how accurate the sample mean is compared to the

true population mean. Larger samples give a more reliable estimate of the true population mean. Reporting data with SE error bars in published articles is typical practice.

148. I have selected some of the SD data in Table 1 and converted them to SE values. My results look like the following. For the BBR group, the sample size is 58. For the placebo group, the sample size is 52. I have compared the SE data point below with Zhang's Figure 3-B. Zhang's Figure 3-B accurately represents the data.

Table 1. Baseline and 3-month clinical characteristics of berberine and placebo groups								
No. (male/female)	Berberine				Placebo			
	58 (30/28)				52 (31/21)			
	Before		After		Before		After	
	SD	SE	SD	SE	SD	SE	SD	SE
Fasting plasma glucose (mmol/liter)	7.0 ± 0.8	7.0 ± 0.1	5.6 ± 0.9	5.6 ± 0.1	6.8 ± 0.9	6.8 ± 0.1	6.4 ± 1.6	6.4 ± 0.2

149. Zhang's clinical trials were performed in a "randomized, double-blind, placebo-controlled" manner in four centers. Bonerge Ex. 1006 (Zhang) at p. 2560 (Study design). This is the type of study that NNB's own expert Dr. Hartung praised as "extremely high quality." NNB Ex. 2028 (Hartung) at 277 ("clinical studies have extremely high quality standards: They are mostly randomized, double-blind, and placebo-controlled, as well as usually multi-centric.").

150. Zhang's findings corroborate at least three prior clinical studies. *See* Bonerge Ex. 1006 (Zhang) at p. 2560 (summarizing clinical research separately by Ni (1988), Xie (2005), and Wei (2004), all reporting enhanced glucose tolerance at daily dosage varying from 900 mg to 1,500 mg). *See* above.
151. Feng concludes that dhBBR is more bioavailable, and "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." Bonerge Ex. 1007 (Feng) at p. 1 (abstract). Based on my review of NNB's expert declarations, NNB's technical experts have not cited a single publication questioning this conclusion.
152. The researchers in Feng conducted extensive *in vitro* human experiments and reported them.
153. The researchers in Feng incubated BBR with *human* intestinal bacteria anaerobically under anerobic conditions to confirm that BBR is metabolized into dhBBR in the intestines. *See* Bonerge Ex. 1007 (Feng) at p. 10 (experimental protocol under "Metabolizing BBR by large intestinal bacteria *in vitro*") and Fig. 1(d)-L. The anerobic condition mimics human gastrointestinal track.

154. The researchers in Feng conducted comparative studies of the intestinal adsorption characteristics of dhBBR and BBR in Caco-2 cell line to prove that dbBBR has better absorption. *See* Bonerge Ex. 1007 (Feng) at p. 12 (experimental protocol under “Absorption of BBR and dhBBR in Caco-2 cells”) and Fig. 3(a). Caco-2 is a human colorectal adenocarcinoma cell line. Caco-2 cells are widely used in pharmaceutical companies for studying drug absorption in humans. NNB Ex. 2175 (Maubon) at p. 659 (“[Caco-2] cells exhibit remarkable morphological and biochemical similarity to the small intestinal columnar epithelium; they are extremely useful for mechanistic studies of drug absorption and are widely used in pharmaceutical companies and the absorption screening assay for pre-clinical drug selection.”)
155. The researchers in Feng incubated dhBBR with *human* intestinal microsomes and with exposure to air to confirm that dhBBR reverts to BBR via oxidization in intestine tissues. *See* Bonerge Ex. 1007 (Feng) at p. 12 (experimental protocol under the “Transformation of dhBBR in pooled human intestinal microsomes (HIMs)”) and Fig. 4(a)-R). Incubation with air exposure can mimic the condition of dhBBR crossing the intestinal epithelium - from the apical / anaerobic intestinal lumen side to the basolateral / blood circulation side.

156. I understand NNB contends two articles on Caco-2 cell line model would “question the human translatability of the Caco-2 cell model.” POR at pp. 47-48. These two articles examine and report differences between Caco-2 cell lines and human intestines. NNB Ex. 2175 (Maubon); NNB Ex. 2176 (Sun).
157. One of the two articles not only acknowledges that Caco-2 cell line is widely used in pharmaceutical companies for studying drug absorption in humans. NNB Ex. 2175 (Maubon) at p. 659. It also concludes that “[c]omparison of Caco-2 cells and small intestine reveals qualitative *similarities* with major transporters present at substantial levels ... which may support the use of Caco-2 cells for investigating intestinal drug transport as already underlined.” NNB Ex. 2175 (Maubon) at pp. 661-662.
158. A POSITA reading Maubon and Sun will not be discouraged from using the Caco-2 cells for human drug absorption studies.
159. Neither Maubon nor Sun would persuade a POSITA to question what Feng teaches, i.e., dhBBR has better intestinal absorption characteristics than BBR, given especially the extensive *in vitro* human experiments and *in vivo* mouse studies reported in Feng. A POSITA would have reasonable expectations that Feng’s finding that dhBBR is more bioavailable is true clinically, not just true at lab studies.

C. Dr. Thomas Hartung

160. I have reviewed Dr. Thomas Hartung's professional resume. NNB Ex. 2107 (Hartung Decl.). Based on my review, Dr. Hartung does not have any background in diabetes, cardiovascular, or metabolic disorder research. Dr. Hartung has not been involved in small molecule drug development such as BBR.
161. Dr. Hartung has not opined whether the experimental protocols in Turner or Feng are defective. As an example, Dr. Hartung has not questioned if the high fat diet rodent models in Turner is an appropriate diabetic model.
162. Dr. Hartung has not opined whether the scientific reasoning in Turner, Zhang, or Feng is sound. As an example, Dr. Hartung has not proposed alternative human intestinal absorption mechanisms for BBR or dhBBR that would undermine a POSITA's reasonable expectations that dhBBR is more bioavailable in humans based on Feng's extensive studies.
163. In one of Dr. Hartung papers, he noted a paper by Hackham and Redelmeier (2006). NNB Ex. 2028 (Hartung) at p. 280. He reports that Hackham reported that 18% of highly cited animal study papers were contradicted by clinical trials, 37% were replicated in clinical trials, and 45% were not tested. NNB Ex. 2028 (Hartung) at p. 280. Because there are more

animal study papers that get replicated by clinical trials than contradicted, the Hackham report indicates a success rate of translating animal studies to clinical trials over 50%.

D. Dr. Qiang Tong

164. Dr. Tong opines that “metabolic disease literature is replete with examples where rodent efficacy failed to translate into clinical benefit in humans, including within the treatment of metabolic disorders.” NNB Ex. 2109 (Tong Declaration) at ¶37. Dr. Tong cites a few literatures in his report as support. NNB Ex. 2109 (Tong Declaration) at ¶¶37-40. Dr. Tong does not analyze these articles to ascertain why rodent efficacy failed to translate into clinical benefit in humans. He does not explain why the failure to translate the rodent efficacy reported in these articles would inform a POSITA to expect failures translating the rodent efficacy data in Turner or Feng to clinical benefits.

165. Prior to 2016, a POSITA already knew that BBR has therapeutic effects on diabetic patients. This is covered in background discussion in papers such as Turner, Zhang, and Feng. As an example, Turner mentions “[BBR’s] therapeutic potential for the treatment of diabetes ... in humans has been reported.” Bonerge Ex. 1004 (Turner) at 1414 (citing footnote 4 publication by Ni which is attached as Bonerge Exhibit 1021). As another

example, Feng mentions that “[t]he therapeutic effect of BBR on lipid- and glucose related metabolic disorders are recently confirmed in a large number of patients by independent clinical groups both in and outside China.”

Bonerger Ex. 1007 (Feng) at p. 2. Because dhBBR gets oxidized to BBR both *in vivo* and *in vitro* (see supra discussion of Feng), a POSITA would have reasonable expectations that translating the rodent efficacy data in Turner or Feng would yield clinical benefits.

166. The mouse strain in the Andrikopoulos experiments is C57BL/6J.

The gender is male. The age is 8 weeks. Bonerger Ex. 1020 (Andrikopoulos) at p. E1324.

167. The mouse strain in the Turner experiments is also C57BL/6J. The gender is male. The age is 6-8 weeks. Bonerger Ex. 1004 (Turner) at p. 1415.

168. Turner performed hyperglycemic clamp tests on rats. Bonerger Ex. 1004 (Turner) at p. 1415, 1418 (Table 1 and corresponding text).

E. “5x More Available” Marketing Slogan

169. The ’961 patent does not teach or disclose dhBBR has 5-fold higher intestinal absorption rate than BBR. The ’961 patent does not mention or

claim that dhBBR is five times more bioavailable than BBR. Bonerge Ex. 1001 ('961 Patent).

170. I have received from counsel several marketing materials. I have been asked to evaluate the technical contents of the marketing material. Based on these marketing materials, I understand that NNB sells dhBBR products under the GlucoVantage® brand. I also understand that NNB touts dhBBR's bioavailability, and repeated claimed that dhBBR is "5x More." See, e.g., NNB Ex. 2115 at p. 011 (dhBBR is "[h]ighly bioavailable form of berberine (up to 5x more effective)); at p. 013 ("The Super Berberine 5x More Bioavailable").

171. I have studied one piece of material consisting of printouts from NNB's websites. NNB Ex. 2115. The website printout includes the following statements with emphasis added. NNB Ex. 2115 at p. 011.

GlucoVantage® (DHB) is a highly bioavailable metabolite of berberine. Essentially, gut microbes reduce berberine into its body-ready form DHB, which is then converted back to berberine after intestinal absorption. Compared to berberine, GlucoVantage® has 5-fold higher intestinal absorption rate, which is due to the fact that berberine has to first be converted to DHB by gut microbes. In essence, GlucoVantage® overcomes the shortcomings of berberine's poor oral bioavailability. In addition, it's been shown that oral administration of antibiotics further suppresses berberine absorption via decreased levels of intestinal microbes, resulting in lower levels of berberine in the blood, which ultimately reduces

efficacy. Simply put, GlucoVantage® is the body-ready form of berberine. While GlucoVantage® works similarly to berberine in terms of stimulating both glucose uptake and AMPK, more importantly, GlucoVantage® can work at lower doses because it bypasses the rate-limiting step of microbial reduction of berberine. GlucoVantage® has been shown to reduce adiposity and improve insulin sensitivity, which helps support healthy glucose tolerance and glycemic control. GlucoVantage® has greater anti-inflammatory, anti-atherosclerotic and hypolipidemic activities than berberine, and it is considered to be more conducive to supporting cardiovascular, metabolic and cerebrovascular health.

172. Based on my studies of Feng and the paragraph above, I have concluded that NNB relied on Feng to support its “5x More” marketing claim on its website. Specifically, the following sentences (highlighted above)

Essentially, gut microbes reduce berberine into its body-ready form DHB, which is then converted back to berberine after intestinal absorption. Compared to berberine, GlucoVantage® has 5-fold higher intestinal absorption rate, which is due to the fact that berberine has to first be converted to DHB by gut microbes ... In addition, it's been shown that oral administration of antibiotics further suppresses berberine absorption via decreased levels of intestinal microbes, resulting in lower levels of berberine in the blood, which ultimately reduces efficacy.

is simply paraphrasing Feng's conclusions. *See* Bonerge Ex. 1007 (Feng) at p. 1 (abstract).

173. Another piece of marketing material I received from counsel is a sponsored internet blog post for GlucoVantage. The blog is available at <https://blog.priceplow.com/supplement-ingredients/glucovantage> (last visited August 27, 2026). I have visited the website. I include a true and correct copy of the printout to my declaration. Bonerge Ex. 1022 (PricePLOW Blog). The sponsored blog is published in January 2020.
174. I have reviewed the contents of the PricePLOW Blog, which include the following statements
- A derivative of berberine, DHB is one of 17 metabolites the parent compound breaks into during its life cycle within the body.^[20] However, the chemical structure of DHB gives it an incredible advantage - DHB is easily absorbed into the intestine, where its then oxidized back into berberine and sent into the plasma!^[20] GlucoVantage acts as the "elusive spy" in your favorite thriller movie - it slips through barriers with ease, doing the work of the good guys behind enemy lines!
- ...
- Research has validated this bioavailability advantage, too. In 2015, scientists compared oral DHB to berberine, at doses that would amount to an equivalent final product. In vitro, they found that the intestinal absorption rate of dihydroberberine was five times higher than berberine.^[20] These findings were then tested in practice on mice, and the researchers found that DHB was better absorbed than berberine, including in the mice lacking the necessary intestinal bacteria needed to break down berberine.^[20]
- ...
20. Feng, Ru, et al; "Transforming Berberine into Its Intestine-Absorbable Form by the Gut Microbiota.";

Nature News; Nature Publishing Group; 15 July 2015;
<https://www.nature.com/articles/srep12155>.

175. Based on my studies of Feng and my review of the Mike Roberto Blog, I have concluded that NNB used Feng to support its “5x More” marketing claim for dhBBR on the internet.

IV. RIGHT TO SUPPLEMENT

176. I reserve the right to supplement my testimony and this report in response to any further judicial determinations, in response to additional arguments expressed by Patent Owner or the opinions of Patent Owner'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.

V. CONCLUSION

I declare that all statements made herein of my own 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 August 28, 2026

By:

Ronald J. Shebuski, Sr.

Ronald J. Shebuski, Sr., Ph.D.