

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

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

v.

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

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

Inter Partes Review No.: IPR2025-01593

PETITIONER'S REPLY BRIEFING

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EXHIBIT LIST

No.	Description
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 .
1023	Supplemental Declaration of Dr. Ronald J. Shebuski, Sr.
1024	Declaration of Hua Chen l in Support of Petitioner's Reply
1025	Ex parte Bernstein, Appeal No. 2014-007316, Appl. No. 13/197,581 (P.T.A.B. Aug. 27, 2015) (Decision on Appeal)
1026	Appellant's Appeal Brief, U.S. Patent Application No. 13/197,581 (Ex parte Bernstein), with Exhibits A-G
1027	Nature's Fusions production, NF00028-NF00033 (HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY; to be filed under seal)
1028	Bonerge Brochure - Berberine and Dihydroberberine Ver-1.0, NF00034-NF00042 (attachment to NF00028) (HIGHLY CONFIDENTIAL - ATTORNEYS' EYES ONLY; to be filed under seal)
1029	Amazon.com product listing for Nature's Fusions dihydroberberine (ASIN B0CWC6F56X), captured August 30, 2026

I. INTRODUCTION

According to NNB, clinical success cannot be predicted because humans and rodents are different, and animal models and in vitro human studies are imperfect. That is the theme of NNB’s non-obviousness arguments. Yet “certainty and absolute predictability are not required to establish a reasonable expectation of success.” *Salix Pharms., Ltd. v. Norwich Pharms., Inc.*, 98 F.4th 1056, 1062 (Fed. Cir. 2024). Where, as here, success is measured against broad claims reciting a dietary supplement at an “approximately 25 mg to approximately 800 mg” dose performing a vague method of “managing glucose tolerance,” a skilled artisan is well-equipped to find obviousness. NNB’s expert declarations never challenge the proofs of principle articles anchoring Petitioner’s invalidity case; rather, they delve into imperfection of the experimental protocols and the complexity of human biology to assert non-obviousness. These reflect merely the garden-variety uncertainty typical of any drug development program, which is legally insufficient.

II. LEGAL STANDARD

A petitioner in an *inter partes* review has the burden of proving a claim’s invalidity by a preponderance of the evidence. *Ariosa Diagnostics v. Verinata Health, Inc.*, 805 F.3d 1359, 1364-65 (Fed. Cir. 2015). Where all limitations are found in multiple references, the petitioner must prove “a skilled artisan would have been motivated to combine the teachings of the prior art references to achieve the claimed

invention, and that the skilled artisan would have had a reasonable expectation of success in doing so.” *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1361 (Fed. Cir. 2007). A finding of “obviousness cannot be avoided simply by a showing of some degree of unpredictability in the art so long as there was a reasonable probability of success.” *Id.* at 1364. “[T]he expectation of success need only be reasonable, not absolute.” *Pfizer Inc. v. Sanofi Pasteur Inc.*, 94 F.4th 1341, 1349 (Fed. Cir. 2024).

III. NNB HAS NOT REFUTED PETITIONER’S PRIMA FACIE CASE OF OBVIOUSNESS BASED ON GROUNDS 1 & 2

Petitioner contends that the claims at issue are obvious in view of Turner and Shaw. Specifically, Turner teaches that both BBR and dhBBR improve glucose tolerance in diabetic rodent models. Turner teaches that dhBBR is more bioavailable. Turner suggested that dhBBR is “an attractive potential therapy for the treatment of type 2 diabetes.” Shaw and FDA Guidance both teach a Body Surface Area conversion method of translating animal dosage to a human dosage for clinical research. Applying the BSA conversion, the rodent dosage in Turner falls within the claimed 25mg-800mg range. *See generally* Pet. at 12-15, 18-27.

The POR rebuttal makes two main arguments. First, Turner has “several substantial experimental design flaws”. POR at 15. Second, Shaw is irrelevant because it is heavily criticized by Blanchard. *Id.* at 18. Neither argument has merit.

A. The alleged “experimental design flaws” in Turner do not refute a motivation to combine nor undermine reasonable expectations of success.

To start, Turner explicitly encourages others to explore dhBBR for diabetes treatment. *See Turner* at 1417 (“dhBBR represents an attractive potential therapy for the treatment of type 2 diabetes...”); *id.* at 1416-1417 (“we have also identified a novel BBR derivative that displays improved in vivo efficacy, thus paving a path for future drug development in this area”) NNB’s experts have not cited a single publication questioning Turner’s conclusion, or discouraging further diabetic research on dhBBR. Ex.1023 (Shebuski Supp. Decl.) ¶116. Rather, they resort to criticizing Turner’s methodology.

NNB’s first “design flaw” criticism relates to the glucose tolerance test setup. Specifically, in the Turner IPGTT test, a glucose load is administered intraperitoneally. As human OGTT is initiated via an oral glucose load, the Turner test skipping the gastrointestinal tract is “physiologically irrelevant”. POR at 15.

NNB overstates the limitation of Turner’s IPGTT test. Turner indicates that dhBBR improves glucose tolerance through enhancing insulin activity for the *whole* body, not through mechanisms localized to the GI tract. Ex.1023 ¶¶117-118. It is the same mechanism by which the diabetic drug metformin exerts its effects on humans, at least in part. *Id.* ¶¶119-120. A POSITA would have reasonable expectations that

Turners' IPGTT test result would translate successfully to humans. *Id.* ¶120.

One related criticism on this issue originates from research done by Andrikopoulos. *Id.* ¶122. While Andrikopoulos shows that the IPGTT and OGTT test results differ, his conclusion is “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.” *Id.* ¶124. Because Turner finds that dhBBR improves glucose tolerance in the same HFD C57BL/6J mouse strain under the less sensitive IPGTT test, Andrikopoulos strengthens a POSITA's expectation of success. *Id.* ¶125.

NNB's second criticism relates to another aspect of the GTT setup - how long the mice were fasted before the test. POR at 15. Specifically, NNB experts contend Turner's overnight fasting protocol is inappropriate because the mouse was in a state of starvation before the test. *Id.* Because Turner indicates that dhBBR improves glucose tolerance due to increased AMPK activity – a conclusion that NNB does not dispute – and activating AMPK is a known mechanism for human diabetes drug, a POSITA would have reasonable expectations that the Turner overnight GTT test result would translate successfully. Ex. 1023 ¶¶121, 126.

Again, Andrikopoulos supports such expectations. Andrikopoulos teaches a test after overnight fasting is not as sensitive as a test following a six-hour fasting. *Id.* ¶127. Because Turner already finds that dhBBR improves mice's glucose tolerance under the less sensitive GTT test, a POSITA would expect the GTT test

under the 6-hour fasting schedule to have more pronounced results. *Id.* ¶128.

NNB's third criticism relates to anesthesia use. POR at 15. This criticism is misplaced. First, Petitioner's obviousness argument is based on the *mouse* GTT test reported on Turner's Fig. 3. Pet. at 19. The experimental protocol for the mouse GTT test does not involve anesthesia. Ex. 1023 ¶129. Second, Andrikopoulos concludes that anesthesia does not affect GTT test results if the experiments are properly controlled. *Id.* ¶130. Turner's experiments are properly controlled. *Id.*

B. A POSITA would have reasonable expectations that BSA-converted human equivalent dosage would be effective.

The human equivalent dosage (HED) for dhBBR converted from Turner is 486 mg/day for an adult weighing 60kg. Pet. at 24, 26. It falls within the claimed range. POR at 32.

1. A POSITA would have reasonable expectations of success of the HED dosage in view of Shaw and the state of the art

NNB contends that a POSITA lacks the motivation to combine Shaw, or there is no reasonable expectation that the HED dosage would be effective. Yet none of NNB's technical experts opines that a POSITA would suspect the 486 mg/day dosage may be pharmaceutically ineffective. Ex. 1023 ¶131. Instead, NNB's argument relies on a review paper that criticizes Shaw. POR at 18-20.

NNB's contention is invalid in view of the state of diabetes research before

the critical date. A POSITA would be motivated and have reasonable expectations that the 486 mg/day HED would be effective despite Blanchard's criticism of Shaw. Ex. 1023 ¶¶132-134. Specifically, A POSITA is unlikely to have underdose or overdose concerns that drive the criticism. *Id.* ¶133.

The state of the art dispels any underdose concerns. A POSITA knew that 1,000 mg/day BBR would be effective. *Id.* ¶135. Further, 100 mg/kg/day dosage of dhBBR was shown to improve mouse's glucose tolerance while a dose of 560 mg/kg/day dosage is needed for BBR. Ex. 1023 ¶136. A POSITA therefore would have reasonable expectations that the 486 mg/day dhBBR dosage is effective. Ex. 1023 ¶134.

Blanchard's overdosing concern is also unwarranted. Before the critical date, a POSITA knew that 1,500 mg/day BBR was safe. *Id.* ¶¶137-138. Even though dhBBR is more bioavailable, a POSITA is unlikely to expect serious adverse effects for the oral dhBBR dose of 486 mg/day, one third of the safe BBR dosage. *Id.* ¶138.

2. *A POSITA would have reasonable expectations of success of using BSA method in view of the FDA Guidance and routine experimentation*

Petitioner supports its argument with FDA Guidance, which NNB dismisses on the grounds that the FDA Guidance "explicitly disclaim any relevance of use of BSA conversion for establishing a pharmacologically active dose." POR at 23.

NNB's reading of what FDA Guidance disclaims is too narrow.

The FDA Guidance states “[i]f 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.” Ex. 1023 ¶139. “HED” means “[a] dose in humans anticipated to provide the same degree of effect as that observed in animals at a given dose.” *Id.* FDA Guidance thus suggests that HED “*can be derived from a PAD*” and *can be useful* in drug development. *Id.* Because Turner discloses *in vivo* dosage, a POSITA would have reasonable expectations that the 486 mg/day HED dosage would provide the “same degree of effect” on humans. *Id.*

Alternatively, if a POSITA follows what FDA Guidance explicitly teaches, he is likely to start dhBBR dosage from 48.6 mg/day. Pet. at 27. If no efficacy is detected, he would escalate. Ex. 1023 ¶140. In view of the state of the diabetic research on BBR and dhBBR, a POSITA would have reasonable expectations that the lowest pharmacologically effective dhBBR dosage will be less than 800 mg. *Id.* In other words, a POSITA would have achieved the claimed range through routine experimentation. *See BioMarin Pharm. Inc. v. Genzyme Therapeutic Prods. LP*, No. IPR2013-00534, Paper 81 at 14 (P.T.A.B. Feb. 23, 2015) (“[D]iscovery of an optimum value of a result effective variable in a known process is ordinarily within the skill of the art.”)

Finally, PTAB precedent clearly refutes NNB's argument that a human dosage

calculated from BSA conversion *cannot* be used to invalidate claims covering dosage regimen. In *Ex parte Bernstein*, Appeal No. 2014-007316 (P.T.A.B. Aug. 27, 2015), the Board affirmed Examiner’s obviousness rejection of several dosage claims on the basis of BSA conversion. Ex. 1024 (Chen Decl.), Ex. 1025 (*Ex parte Bernstein* Decision) at 8. Specifically, the panel credited the Examiner’s finding that a POSITA “would have found it routine to calculate a reasonable human dosage based on [and] mouse dosage, and would further have found guidance in Murdock’s discussion of the Freireich’s work, which takes into account the interrelationship of animal size and species.” Ex. 1025 at 8. The Applicant made the same argument NNB makes here- BSA conversion does not indicate efficacy. *See* Ex. 1024, Ex. 1026 (*Bernstein Appeal Br.*) at 11 (“The Freireich calculation indicates nothing about the effective dose or safety of effective doses in humans.”). The Applicant used the same 2005 FDA Guidance (attached as Exhibit G to his brief), to no avail, to “explain” why BSA conversion does not indicate efficacy. *Id.* This panel should similarly reject NNB’s arguments.

C. NNB has not refuted Petitioner’s Prima Facie case of obviousness against all Dependent Claims

NNB’s rebuttal arguments for dependent claims do not refute Petitioner’s prima facie case for reasons stated in the Petition and here. Specifically for dependent claim 2, NNB’s rebuttal arguments are based on a claim construction

position unsupported by the specification. Pet. at 10–11. If this Panel adopts NNB’s claim construction, Petitioner submits that the prior art disclosure of BBR’s ability to improve “fasting glucose levels,” *see* Ex. 1021 (Ni) entitled “Therapeutic effect of berberine on 60 patients with Type II diabetes mellitus and experimental research,” which is cited as Fn. 4 in Turner, combined with Turner’s indication that dhBBR being an “effective vehicle for delivering BBR to the circulation” would have rendered this claim obvious. Ex. 1003 ¶¶91, 93; Pet. at 55.

IV. NNB HAS NOT REFUTED PETITIONER’S PRIMA FACIE CASE OF OBVIOUSNESS BASED ON GROUNDS 3 & 4

With respect to grounds 3 and 4, Zhang teaches that berberine taken 1,000 mg/day is effective and safe in treating type 2 diabetes. Feng teaches that dhBBR has a much higher intestinal absorption rate, and that dhBBR gets converted back to BBR after absorption in intestine tissues and enters the blood. A POSITA thus would be motivated to investigate dhBBR for diabetes treatment due to its bioavailability. Moreover, the POSITA would have a reasonable expectation of success. *See generally* Pet. at 15–17, 43–48.

NNB attacks from two angles. First, it asserts Zhang is not reliable because it includes “questionable representation of data and statistical significance related to Fig. 3B ...” POR at 42. Second, it asserts Feng is “immaterial” because Feng’s findings came from studies done “under lab conditions.” *Id.* 44. Neither argument

withstands scrutiny.

A. NNB's accusation of Zhang is baseless

Central to NNB's criticism is the allegation that the "error bars" depicted Zhang's Fig. 3B do not represent the $\pm$ deviation data reported in Table 1. *Id.* 39-42. NNB illustrates this alleged "significant[] and inexplicabl[]" difference via a side-by-side comparison of the published Fig. 3B versus a "corrected" Fig. 3B. *Id.* According to NNB, "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." *Id.* 42.

NNB's attack is misguided; Zhang's data is represented accurately. Ex. 1023 ¶143. Table 1 data is in "mean $\pm$ SD" format. The error bars in Fig. 3B are in " $\pm$ SE" format. $SE = SD/\sqrt{n}$ where n is the sampling size. *Id.* ¶¶144-146. Standard Deviation describes how spread out the individual data points are around the mean; Standard Error measures how accurate the sample mean is compared to the true population mean. Using SE error bars is typical practice. *Id.* ¶147. Using the sample sizes in Table 1, the SD and SE numbers would look like the following. *Id.* ¶148.

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 $\pm$ 0.8	7.0 $\pm$ 0.1	5.6 $\pm$ 0.9	5.6 $\pm$ 0.1	6.8 $\pm$ 0.9	6.8 $\pm$ 0.1	6.4 $\pm$ 1.6	6.4 $\pm$ 0.2

Figure 3-B accurately represents the data. NNB's accusation is baseless.

In fact, there are many reasons a POSITA would trust Zhang, including its “extremely high quality” clinical trials that Dr. Hartung would have praised, and corroboration by at least three prior clinical studies. Ex. 1023 ¶¶149–150. Most telling is NNB’s failure to identify a single article that disparages Zhang’s conclusion that BBR is effective and safe for diabetes treatment at 1,000 mg/day. *Id.* ¶142.

B. Feng would have motivated a POSITA to conduct clinical diabetic studies on dhBBR with reasonable expectations of success

Petitioner’s obviousness argument is based on Feng’s research confirming dhBBR’s bioavailability, and Feng’s conclusion that “gut microbiota reduces BBR into its absorbable form of dhBBR, which then oxidizes back to BBR after absorption in intestine issues and enters the blood.” Ex. 1007 (Feng), abstract. Again, NNB’s experts have not identified a single publication questioning Feng’s conclusions. Ex. 1023 ¶151.

NNB contends instead that Feng’s findings cannot be expected to translate to humans because its *in vitro* human and *in vivo* animal studies are done “under lab conditions” thus “immaterial.” POR at 44. Feng falls short because “Feng did not provide any data from whole-bodied humans.” *Id.* 45. Following NNB’s logic, nothing short of a clinical dhBBR trial may render the ’961 claims obvious.

“[O]ur case law makes clear that ... a showing of a reasonable expectation of success in a method of treatment claim need not rely on clinical data....” *See Eli*

Lilly & Co. v. Teva Pharms. Int'l GmbH, 8 F.4th 1331, 1346 (Fed. Cir. 2021). *Accord Ex parte Bernstein* (affirming examiner's obviousness rejection of a method claim based on "a proof of principle paper" from in vivo mouse studies); *Genzyme Therapeutic Prods. L.P. v. Biomarin Pharm. Inc.*, 825 F.3d 1360, 1372-73 (Fed. Cir. 2016). Genzyme presented arguments similar to NNB's. *Id.* at 1364 ("because all of the combinations of references described *in vitro* experiments, a person of ordinary skill would not find those experiments predictive of results in a human patient"); BioMarin, No. IPR2013-00534, Paper 81 at 20 (there are "complications that arise when transitioning from an *in vitro* model to an *in vivo* model.") Neither the PTAB nor the CAFC was persuaded.

NNB also mischaracterizes what Feng teaches. Its criticism ignores the extensive *in vitro* human experiments reported. Ex. 1023 ¶152. Specifically, Feng incubated BBR with *human* intestinal bacteria anaerobically. *Id.* ¶153. They conducted comparative studies of the intestinal adsorption characteristics of dhBBR and BBR in Caco-2 cell line. *Id.* ¶154. The cell line is widely used in pharmaceutical companies for studying drug absorption in humans. *Id.* The researchers also incubated dhBBR with *human* intestinal microsomes. *Id.* ¶155.

Viewing these experiments as a whole, it is difficult to understand NNB's assertion that "[n]o evidence ... was shown in Feng to indicate the same conversion takes place in living human's microbiome, or to lead a POSITA to even reasonably

expect that it would, given the substantial differences between rodent and human microbiomes.” POR at 44. This statement from Dr. Kerksick is ambiguous. NNB Ex.2108 (Kerksick Decl.) ¶83. If it means that Feng does not report *any* human microbiome experiments showing dhBBR-BBR conversion, Dr. Kerksick is wrong. Feng conducted *in vitro* human microbiome experiments. If it means Feng has not performed clinical human microbiome studies to show conversion, Dr. Kerksick’s opinion, while technically accurate, becomes irrelevant because “certainty and absolute predictability are not required to establish a reasonable expectation of success.” *Salix*, 98 F.4th at 1062.

NNB’s additional attempts to discredit Feng are also misguided. Chief among them is the generalized statements of substantial difference between rodent and human gut microbiomes. Generalized assertions of unpredictability in the art, without more, cannot rebut a prima facie case of obviousness. *Accord Mylan Pharms. Inc. v. Sanofi-Aventis Deutschland GmbH*, No. IPR2017-01526, Paper 89 at 37 (P.T.A.B. Dec. 12, 2018). Because Feng’s findings are supported by both rodent *and* human gut microbiomes studies, these generalized differences are even more irrelevant.

NNB also cites two articles that examine and report differences between Caco-2 cell lines and human intestines, implying data from Caco-2 cell models are not translatable to humans. POR at 47-48. But neither article discourages using

Caco-2 cells to study human intestine drug absorption. In fact, the Maubon article concludes that the two have “qualitative similarities.” Ex. 1023 ¶¶157-158. In view of the extensive *in vitro* and *in vivo* human and mouse studies Feng reported, a POSITA would have reasonable expectations that Feng’s finding that dhBBR is more bioavailable is true clinically, not just at lab studies. *Id.* at ¶159.

In short, NNB has not presented any evidence that challenges Feng’s conclusion that dhBBR is more bioavailable, and that dhBBR is oxidized into BBR and enters blood. *Id.* ¶¶151, 159. From these principles, a POSITA would have reached the claimed dosage of 25mg-800mg of dhBBR in view of Zhang combined with Feng through routine experimentation.

V. NNB’S ADDITIONAL LACK OF MOTIVATION TO COMBINE ARGUMENTS FAIL

NNB contends that the eight-year lapse between Turner and the ’961 invention evidences lack of motivation to combine. POR at 54-56. This argument is not supported by the law. “Absent a showing of long-felt need or the failure of others, the mere passage of time without the claimed invention is not evidence of nonobviousness.” *Iron Grip Barbell Co. v. USA Sports, Inc.* 392 F.3d 1317, 1324-1325 (Fed. Cir. 2004). The case NNB cites applied the same standard. *See Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1358-59 (Fed. Cir. 2013) (finding non-obviousness based in part on “extensive experimental evidence of unexpected

results”).

NNB has not presented any evidence of unexpected results, or failure of others. In fact, there are no reported dhBBR clinical trials before the critical date according to NNB’s expert. NNB Ex.2109 (Tong Decl.) ¶¶33-34.

For reasons stated in Section VII.B *infra*, NNB has not presented any legally sufficient evidence of a long-felt need either.

VI. NNB’S ADDITIONAL LACK OF REASONABLE EXPECTATION OF SUCCESS ARGUMENTS FAIL

A. Dr. Hartung’s generalized non-obviousness opinion is irrelevant or unreliable

Dr. Hartung makes a macro-level assertion that “approximately 95% of drug candidates that enter clinical development ultimately fail ...” and “humans and rats are very different.” POR at 57. Dr. Hartung’s opinion is irrelevant because it does not address Petitioner’s obviousness rationale. Dr. Hartung is not an expert in the subject area. Ex. 1023 ¶160. He does not have expertise to criticize the science in the prior art references. He has offered none. *Id.* ¶¶161-162.

With respect to Hartung’s macro-level criticism, his paper belies his bold assertion of “a 90-95% expectation of failure.” POR at 59. In his review paper, Dr. Hartung cites another paper reporting 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. This implies a success rate over 50%. Ex. 1023 ¶163. Dr. Hartung notes this “not too bad” statistics is applicable only to “highly cited studies.” NNB Ex.2028 (Hartung) at p. 280). Yet, he has never analyzed the journal impacts of Turner or Feng. To put it bluntly, Dr. Hartung’s generalized opinion is unreliable.

B. Dr. Kerksick’s opinion regarding the gut microbiota differences between Rodent and Humans does not refute reasonable expectations of success

Dr. Kerksick makes the same non-obviousness arguments by noting “substantial differences in the gut microbiota between rodents and humans”. POR at 60. He flags Feng and opines that there is “no data that [he] observed in Petitioner’s submission showing that the same dhBBR to BBR conversion [Feng reports] happens in the human microbiome.” NNB Ex.2108 ¶83. For reasons stated above, Dr. Kerksick’s criticism fails. *See supra* § IV.B.

C. Dr. Tong’s opinion does not refute reasonable expectations of success

Dr. Tong’s opinion repeats the rodents-are-different theme. He opines that “metabolic disease literature is replete with examples where rodent efficacy failed to translate into clinical benefit in humans” and identifies a few supporting articles. POR at 60-61; *see* NNB Ex.2109 ¶¶37-40. He does not analyze these articles to

ascertain why their rodent efficacy fails to translate into clinical benefits. Ex. 1023 ¶164. More importantly, he does not explain why the failure in these cherry-picked articles would inform a POSITA to expect failures translating Turner or Feng. *Id.* Because Turner/Feng’s teachings on dhBBR were disclosed when a POSITA already knew BBR, its oxidized form, has clinical effects, there are reasonable expectations that translating the rodent efficacy data in Turner or Feng would yield clinical benefits. Ex. 1023 ¶165. Dr. Tong’s generalized skepticism will not suffice.

Finally, Dr. Tong steers criticisms to Turner based on a Fergusson article, focusing on the mouse strain it used and the purported absence of a hyperglycemic clamp test. POR at 61; NNB Ex.2109 ¶¶46-47. Dr. Tong’s criticism is unpersuasive. Regarding the former, the Andrikopoulos reference used the same mouse strain, the same gender, and similar age. Ex. 1023 ¶¶166-167. Clearly, the mouse strain and the cohort Turner picked is an informative pathological model. Regarding the latter, Dr. Tong *wrongfully* asserts that Tuner “did not ... use the ‘gold standard’ hyperglycemic clamp test discussed in Fergusson on the mice or *rats* in the study.” NNB Ex.2109 ¶47 (emphasis added). Turner did, in fact, perform the gold standard test on rats. Ex. 1023 ¶168.

VII. NNB’S OBJECTIVE EVIDENCE OF NON-OBVIOUSNESS DOES NOT OVERCOME THE PRIMA FACIE CASE

Objective evidence of non-obviousness includes the following types:

“commercial success, industry praise, unexpected results, copying, industry skepticism, licensing, and long-felt but unsolved need.” *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling USA, Inc.*, 699 F.3d 1340, 1349 (Fed. Cir. 2012). “The patentee bears the burden of showing that a nexus exists between the claimed features of the invention and the objective evidence offered to show non-obviousness.” *WMS Gaming, Inc. v. Int’l Game Tech.*, 184 F.3d 1339, 1359 (Fed. Cir. 1999).

The evidence NNB proffered relates merely to three factors - commercial success, long-felt but unsolved need, and industry praise. They are inadequate.

A. NNB has not met its burden of proving commercial success of the ’961 claims at issue

NNB has failed to demonstrate the nexus between the alleged commercial success of dhBBR and the ’961 claims at issue for at least the following reasons.

First, NNB’s expert Mr. Holzen’s opinion on nexus is not supported by actual evidence. The “nexus” analysis portion of his opinion does not provide evidentiary cites. NNB Ex.2181 (Holzen Decl.) ¶¶76-78. It can be inferred that he relies on the marketing materials exhibits as supply side evidence, and consumer review feedback as demand side evidence. *Id.* ¶67.

A deeper analysis of the exhibits and online evidence Petitioner independently collects exposes Mr. Holzen’s errors, which is most pronounced with respect to the

marketing slogan adopted by both NNB and its competitor – dhBBR is “5x more” bioavailable. *See id.* ¶50; NNB Ex.2115 at 011 (dhBBR is a “[h]ighly bioavailable form of berberine (up to 5x more effective)”); NNB Ex.2124 at 012 (Dihydroberberine “has shown to be up to 5x more bioavailable/absorbable.”); NNB Ex.2124 at 016 (consumer commenting “Glucovantage® is more bioavailable”); Ex. 1029 (Nature’s Fusions Amazon Listing) at 1 (product label image displaying “5x More Bioavailable**”).

Mr. Holzen’s nexus opinion is fatally flawed because he failed to trace the basis of the “5x more” claim. This heavily promoted feature derives from Petitioner’s 103 prior art – Feng. *See Ormco Corp. v. Align Tech., Inc.*, 463 F.3d 1299, 1312 (Fed. Cir. 2006) (“if the feature that creates the commercial success was known in the prior art, the success is not pertinent.”). In contrast, the ’961 patent never teaches that dhBBR is 5 times more bioavailable. Ex. 1023 ¶169.

NNB used Feng to support the “5x more” marketing claim. For example, a sentence NNB publishes on its website reads the following: “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.” *See* NNB Ex.2115 at 011. Additional statements touting dhBBR’s bioavailability merely paraphrase what Feng teaches. Ex. 1023 ¶¶171-172.

If there is any doubt that NNB is not using Feng to market dhBBR’s

bioavailability, such doubt is dispelled by a blog NNB sponsored for its GlucoVantage[®] product. *Id.* ¶¶173-175; Ex. 1022 (PricePlow Blog) at 007 (“In vitro, [the Feng researchers] found that the intestinal absorption rate of dihydroberberine was five times higher than berberine.”).

Petitioner and its customer also relied on Feng to make the “5x More” marketing claim. Petitioner’s marketing material and Nature’s Fusions’ subpoena production¹ made it clear. *See* NNB Ex.2119 (Bonerge website) at 008 (citing Feng for the marketing claim that “Dihydroberberine can be absorbed more rapidly by the intestinal wall, resulting in higher bioavailability compared to Berberine.”). *See also* Ex. 1028 (Bonerge brochure attached to email to Nature’s Fusions) at NF00039 (stating “In a study (Ru Feng et al. 2015), researchers compared oral dihydroberberine to standard berberine. In vitro, they discovered that DHB's internal absorption rate was five times greater than BBR’s.”); Ex. 1024 at ¶¶6-7.

Finally, Mr. Holzen failed to credit non-claimed features to alleged commercial success. Consumers have commented on dhBBR’s “lack of odor” as an appealing feature. *See* NNB Ex.2115 at 015. “Longer-lasting” is another marketing feature that is appealing. NNB Ex.2124 at 012, 016 (consumer comments). The

¹ Ex. 1024 (Chen Decl.) at ¶¶5-7.

Amazon listings also tout non-claimed features. For example, one feature on Nature's Fusions' product label image is "Cardiovascular Support." Ex. 1029 (Nature's Fusions Amazon Listing, captured August 31, 2026) at 1, which is not a claimed '961 feature. *See Owens Corning v. Certainteed Corp.*, No. IPR2014-01403, Paper 35 at 32 (P.T.A.B. Mar. 8, 2016) (where "any commercial success may be attributable, at least in part, to unclaimed features or features known in the prior art, Patent Owner has not established a nexus between any commercial success and the claimed invention").

1. BBR's Nature Ozempic Fame Disproves NNB's Commercial Success claim for dhBBR

NNB's own exhibits show that BBR has gained tremendous popularity as "Nature's Ozempic" due to TikTok notoriety on or around mid-2023. *See* NNB Ex.2113 at 009 (July 31, 2023 wired.com story observing that "Berberine went viral as a weight loss wonder pill"); NNB Ex.2130 at 001 (June 20, 2023 GQ.com story reporting "Videos tagged with 'berberine' have eclipsed 100 million views on TikTok, where it's now being called 'nature's Ozempic.'"). Mr. Holzen claims that dhBBR has achieved "disproportionate commercial success" that cannot be explained by BBR's TikTok fame alone. NNB Ex.2181 ¶102.

Mr. Holzen's "disproportionate commercial success" claim is not supported because he cites unreliable data and his analysis lacks rigor. NNB sells raw

ingredients. *Id.* ¶23. Persistence Market Research (PMR)’s BBR sales estimate reports cover BBR supplements, not raw material. NNB Ex.2132 at 053. This is an apple versus oranges comparison. Most importantly, Mr. Holzen has not evaluated the reliability of the PMR reports. The reports contradict each other. In one report, the 2022 global BBR market is estimated between \$215M and \$317M with the North America market less than \$150M. *Id.* 028-029. In another report, the 2022 global BBR market is estimated to be \$885M and the North America market is about \$351.3M. *Id.* 053, 057 There is more than a two-fold difference on data from the same marketing firm. Furthermore, one would expect that the 2023 TikTok fame would have spiked the BBR sales in 2023. Yet the reports only predict a modest 8.4% increase – from \$351.3 mil (2022) to \$380.7 mil (2023). *Id.* 057. The PMR data is simply untrustworthy. *Accord Chemipal Ltd. v. Slim-Fast Nutritional Foods Int’l, Inc.*, 350 F. Supp. 2d 582, 592 (D. Del. 2004) (excluding damage expert’s opinion on the size of the “slimming products market” because the expert “does not understand the methodology used to gather the information in the Grey 1997 Plan or the methodology used by those who performed the research for the secondary sources [relied upon by the Grey 1997 Plan]”).

To compound Mr. Holzen’s errors, his analysis of NNB’s dhBBR sales trend is dubious. Here, Mr. Holzen touts NNB’s dhBBR annual revenue growth rate is over 90% CAGR. NNB Ex.2181 at ¶102 . His use of Compound Annual Growth

Rate masks the real trend. Using the annual sales number that Mr. Holzen compiled in ¶84 of his report, NNB's dhBBR sales revenue grew by ~76% from 2021 to 2022 (\$370K to \$651K). It grew by ~256% from 2022 to 2023. The 2023 to 2024 growth dropped to ~113%. The 2024 to 2025 growth rate dropped to ~36%. *Id.* at ¶84. This trend does not reflect a growing market presence. In fact, because the extraordinary 2022-2023 spike correlates with the timing of the BBR TikTok fame, the logical explanation is that dhBBR piggybacked on BBR's success.

B. The Patent Owner has not met its burden of proving long felt but unresolved need

The evidence NNB proffered also fails to prove a nexus between long felt but unresolved need and the '961 claims at issue. Here, NNB cites general journal articles comments on continuing needs for new blood glucose control methods. POR at 65–66. Yet a nexus cannot be satisfied by a general need for more medicine for health deficiency. *See ImmunoGen, Inc. v. Vidal*, 653 F. Supp. 3d 258, 303 (E.D. Va. 2023), *aff'd sub nom. ImmunoGen, Inc. v. Stewart*, 130 F.4th 1328 (Fed. Cir. 2025) (holding that nexus is missing between long-felt need for anti-cancer drugs for a specific cancer and the claim language reciting dosing regimen of a specific cancer drug).

NNB next cites as support general complaints about BBR's poor absorption problem. Yet the absorption issue is resolved by prior art such as Feng. "[O]nce

another supplied the key element, there was no long-felt need or, indeed, a problem to be solved.” *Newell Companies, Inc. v. Kenney Mfg. Co.*, 864 F.2d 757, 768 (Fed. Cir. 1988). In contrast, the ’961 Patent does not teach or claim that dhBBR is five times more bioavailable than BBR. Ex.1023 ¶169.

Most critically, NNB’s argument is contradicted by its sales data. The ’961 patent issued in May 2019. NNB launched GlucoVantage® in 2019. NNB’s consultant promoted dhBBR’s superior bioavailability as early as January 2020. Ex.1022. Yet the GlucoVantage® sales spiked four years later in 2022-2023, apparently in response to BBR’s TikTok fame. There is a four-year delay for NNB’s customers to buy the raw material much more significantly. The long delay belies NNB’s long-felt need assertion. *See Mylan Pharms. Inc. v. Sanofi-Aventis Deutschland GmbH*, No. IPR2018-01684, Paper 79 at 43 (P.T.A.B. May 29, 2020) (“Establishing a long-felt need requires objective evidence that the invention has provided a long-awaited, widely accepted, and *promptly adopted solution* to a problem existent in the art, or that others had tried but failed to solve that problem.”) (emphasis added).

To summarize, the PO has not met its burden of proof that there is a long felt but unmet need of the claimed ’961 features.

C. NNB has not met its burden of proving industry praise

The three exhibits NNB proffered do not support its claim of industry praise.

Exhibit 2173 – does not contain praises. It is a bare citation of the work done by NNB. *Accord Bayer Healthcare Pharms., Inc. v. Watson Pharms., Inc.* 713 F.3d 1369, 1377 (Fed. Cir. 2013) (“bare journal citations ... fall well short of demonstrating true industry praise”). Exhibit 2166 is a journal article. Its “true breakthrough” praise is reserved for third party research validating dhBBR’s greater bioavailability “in both animal studies and human pharmacokinetic trials.” NNB Ex.2166 at 004. There is no nexus to the ’961 invention. Exhibit 2171 is a blog post sponsored by NNB. “Such bare journal citations and self-referential commendation fall well short of demonstrating true industry praise.” *Bayer*, 713 F.3d at 1377.

DATE: August 31, 2026

Respectfully submitted,

/s/ *John Handy*

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CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24, the undersigned certifies that this Petitioner's Reply Briefing contains 5,595 words, excluding the parts of the paper exempted by 37 C.F.R. § 42.24(a)(1) and the signature block), as measured by the word-processing system used to prepare this paper and counting the 32 words in the table image on page 10 separately. The limit under 37 C.F.R. § 42.24(c)(1) is 5,600 words.

DATE: August 31, 2026

Respectfully submitted,

/s/ John Handy

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CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this PETITIONER'S REPLY BRIEFING, together with Exhibits 1020-1029 filed herewith, has been served on August 31, 2026 upon the following counsel of record for Patent Owner via electronic means:

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