

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*

**PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S
RESPONSE TO PETITION**

Pursuant to 37 C.F.R. § 42.120, Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. hereby respectfully submits its Patent Owner Response to Bonerge Lifescience (Hunan) Co., Ltd.'s Petition for inter partes review of claims 1, 2, 3, 5, 6, and 7 of U.S. Patent No. 10,278,961.

TABLE OF CONTENTS

I.	INTRODUCTION	1
II.	BACKGROUND	1
	A. Brief Background of U.S. Patent 10,278,961	1
III.	CLAIM CONSTRUCTION	3
IV.	PETITIONER’S OBVIOUSNESS CHALLENGES EACH FAIL ON THE MERITS.....	8
	A. Legal Standard for Obviousness	8
	1. <i>Graham</i> Factors.....	8
V.	THE LEVEL OF ORDINARY SKILL IN THE ART	12
VI.	THE SCOPE AND CONTENT OF THE PRIOR ART DOES NOT TEACH THE CLAIM LIMITATIONS AS REQUIRED	14
	A. Ground 1: Claims 1, 2, 5, 6, and 7 are Not Obvious in light of Turner in View of Shaw	14
	1. Turner	14
	2. Shaw	17
	3. Additional References Included by Petitioner in Ground 1	24
	4. Claim Charts for Ground 1	29
	B. Ground 2: Claim 5 is Not Obvious in light of Turner in View of Shaw and Further in View of Zhang	38
	1. Zhang Reference (also applicable to Grounds 3, 4)	38
	2. Claim Chart for Ground 2	43
	C. Ground 3: Claims 1, 2, 5, and 7 are Not Obvious in light of Zhang in View of Feng	43
	1. Zhang:	43
	2. Feng.....	44
	3. Claim Charts for Ground 3	45

	D.	Ground 4: Claim 6 is Not Obvious in light of Zhang in View of Feng Further in View of Turner.....	53
VII.		ADDITIONAL POINTS SUPPORTING THE ABSENCE OF A MOTIVATION TO COMBINE OR MODIFY THE PRIOR ART.....	54
VIII.		ADDITIONAL POINTS SUPPORTING THE ABSENCE OF A REASONABLE EXPECTATION OF SUCCESS.....	56
	A.	Dr. Thomas Hartung Opines That There is no Reasonable Expectation of Success	57
	B.	Dr. Chad M. Kerksick Opines That There is no Reasonable Expectation of Success	60
	C.	Dr. Qiang Tong Opines That There is no Reasonable Expectation of Success	60
IX.		SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS FURTHER DEMONSTRATE THE PATENTABILITY OF THE CHALLENGED CLAIMS	62
	A.	Legal Standard.....	62
	B.	The Invention Claimed in the ‘961 Patent is a Commercial Success .	63
	C.	The Invention Claimed in the ‘961 Patent Addressed a Long-Felt but Unsolved Need	65
	D.	The Invention Claimed in the ‘961 Patent Received Industry Praise .	67
X.		CONCLUSION.....	70

TABLE OF AUTHORITIES

Cases

<i>Abbott Laboratories v. Andrx Pharmaceuticals, Inc.</i> , 452 F. 3d 1331 (Fed. Cir. 2006)	10
<i>Active Video Networks, Inc. v. Verizon Communications, Inc.</i> , 694 F.3d 1312 (Fed. Cir. 2012)	11
<i>Airbus S.A.S. v. Firepass Corp.</i> , 941 F.3d 1374 (Fed. Cir. 2019)	9
<i>Amgen, Inc. v. F. Hoffman-La Roche Ltd.</i> , 580 F.3d 1340 (Fed. Cir. 2009)	12
<i>Apple, Inc. v. Samsung Electronics Co., Ltd.</i> , 839 F.3d 1034, 1048 (Fed. Cir. 2016)	62, 65
<i>ATD Corp. v. Lydall, Inc.</i> , 159 F.3d 534 (Fed. Cir. 1998)	10
<i>Axonics, Inc. v. Medtronic, Inc.</i> , 73 F.4 th 950 (Fed. Cir. 2023)	11
<i>Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.</i> , 229 F.3d 1120, 1130 (Fed. Cir. 2000)	passim
<i>Chemours Company FC, LLC v. Daikin Industries, Ltd.</i> , 4 F.4 th 1370 (Fed. Cir. 2021)	24
<i>Elekta Ltd. v. ZAP Surgical Sys., Inc.</i> , 81 F.4 th 1368 (Fed. Cir. 2023)	12
<i>Eli Lilly & Co. v. Teva Pharms. Int'l GmbH</i> , 8 F.4 th 1331 (Fed. Cir. 2021)	9, 12
<i>Ferring B.V. v. Watson Labs., Inc.-Fla.</i> , 764 F.3d 1382 (Fed. Cir. 2014)	6
<i>Graham v. John Deere Co.</i> , 383 U.S. 1 (1966)	8, 62
<i>In re Bigio</i> , 381 F.3d 1320 (Fed. Cir. 2004)	9, 25
<i>In re GPAC</i> , 57 F.3d 1573, 1580 (Fed. Cir. 1995)	63
<i>In re Gurley</i> , 27 F.3d 551 (Fed. Cir. 1994)	11
<i>In re Kahn</i> , 441 F.3d at 977 (Fed. Cir. 2006)	11
<i>In re Magnum Oil Tools International, Ltd.</i> , 829 F.3d 1364 (Fed. Cir. 2016)	8
<i>Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.</i> , 821 F.3d 1359 (Fed. Cir. 2016)	12
<i>Kinetic Concepts, Inc. v. Smith & Nephew, Inc.</i> , 688 F. 3d 1342 (Fed. Cir. 2012)	11
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398, 406 (2007)	8
<i>Leo Pharmaceutical Products, Ltd. v. Rea</i> , 726 F.3d 1346, 1355 (Fed. Cir. 2013)	55

<i>Liebel-Flarsheim Co. v. Medrad, Inc.</i> , 358 F.3d 898 (Fed. Cir. 2004)	5
<i>MBO Laboratories, Inc. v. Becton, Dickinson & Co.</i> , 474 F.3d 1323 (Fed. Cir. 2007)	5
<i>Medichem, S.A. v. Rolabo, S.L.</i> , 437 F.3d 1157 (Fed. Cir. 2006).....	9, 11
<i>Merck & Co. v. Teva Pharms. USA, Inc.</i> , 395 F.3d 1364 (Fed. Cir. 2005).....	6
<i>Mintz v. Dietz & Watson, Inc.</i> , 679 F.3d 1372 (Fed. Cir. 2012).....	9, 10
<i>Pall Corp. v. Micron Separations, Inc.</i> , 66 F.3d 1211 (Fed. Cir. 1995).....	6
<i>Phillips v. AWH Corp.</i> , 415 F.3d 1303 (Fed. Cir. 2005)	3
<i>Procter & Gamble Co. v. Teva Pharms. USA, Inc.</i> , 566 F.3d 989 (Fed. Cir. 2009).	9
<i>Securitypoint Holdings, Inc. v. U.S.</i> , 129 Fed.Cl. 25, 39 (Fed. Cl. 2016)	33
<i>Source Search Techs., LLC v. LendingTree, LLC</i> , 588 F.3d 1063 (Fed. Cir. 2009)	10
<i>Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling U.S., Inc.</i> , 699 F.3d 1340, 1349-56 (Fed. Cir. 2012).....	62
<i>Volvo Penta of the Americas, LLC v. Brunswick Corp.</i> , 81 F.4 th 1202, 1210 (Fed. Cir. 2023)	63
<i>W.L. Gore & Assoc., Inc. v. Garlock, Inc.</i> , 721 F.2d 1540 (Fed. Cir. 1983).....	24
<i>Yita LLC v. MacNeil IP LLC</i> , 69 F.4 th 1356, 1365 (Fed. Cir. 2023).	63

Statutes

35 U.S.C. § 103	8, 9, 10, 25
37 CFR §42.100	3
MPEP § 2141.01	9
MPEP § 2143.02	12

TABLE OF EXHIBITS

EXHIBIT NUMBER	DESCRIPTION
2111	Petition for Inter Partes Review of U.S. Patent No. 10,278,961, September 26, 2025; https://assignmentcenter.uspto.gov/search/patent/abstract%3FpatentNumber%3D10278961
2112	https://pubmed.ncbi.nlm.nih.gov/27671811/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC3504405/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC4502414/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC8378955/ ; https://pmc.ncbi.nlm.nih.gov/articles/PMC8746601/ ; https://www.ncbi.nlm.nih.gov/books/NBK564659/
2113	https://www.nccih.nih.gov/health/in-the-news-berberine ; https://www.washingtonpost.com/wellness/2023/06/20/berberine-weight-loss-natures-ozempic/ ; https://www.wired.com/story/berberine-social-media-trend ; https://www.fda.gov/consumers/consumer-updates/fda-101-dietary-supplements
2114	https://dsld.od.nih.gov/label/282103 ; https://dsld.od.nih.gov/label/293642 ; https://dsld.od.nih.gov/label/310819 ; https://dsld.od.nih.gov/label/60586 ; https://ods.od.nih.gov/factsheets/Chromium-Consumer/
2115	https://www.nnbnutrition.com/ ; https://www.nnbnutrition.com/about ; https://www.nnbnutrition.com/gluco-vantage-a-gentle-solution-for-metabolic-health ; https://www.nnbnutrition.com/ingredientology/ ; https://www.nnbnutrition.com/ingredients/gluco-vantage/ ; https://www.nnbnutrition.com/ingredients/gluco-vantage/gluco-vantage/ ; https://www.nnbnutrition.com/patents/ ; https://www.nnbnutrition.com/true-innovation-for-brands/ ; https://web.archive.org/web/20250808201651/https://www.nnbnutrition.com/patents
2116	https://www.nature.com/articles/srep12155
2117	https://www.mdpi.com/2072-6643/14/1/124

2118	https://www.mareksupplements.com/products/berberine
2119	https://www.bonerge.com/about-bonerge ; https://www.bonerge.com/branded-ingredients ; https://www.bonerge.com/branded-ingredients/dihydroberberine ; https://www.bonerge.com/news/natural-products-west-anaheim-longevity-fisetin ; https://www.bonerge.com/odm-cdmo ; https://www.bonerge.com/research-articles/dihydroberberine-vs-berberine-benefits-bioavailability
2120	https://prlabs.com/premier-glucose-manager.html ; https://www.nutraingredients.com/Article/2026/02/16/glp-1-boom-spurs-supplement-innovation-as-bragg-expands-into-metabolic-health/
2121	https://www.organicpowdersupply.com/dihydroberberine-dhb-bulk-powder/ ; https://www.conscientia-industrial.com/plant-extracts/berberine-hydrochloride-cas-633-65-8
2122	https://uspto.report/TM/87004949 ; https://uspto.report/TM/88477171 ; https://tmsearch.uspto.gov/search/search-results/98638859
2123	https://www.walmart.com/ip/Berberine-HCL-500mg-120-Capsules-Barberry-Extract-Supplement-Non-GMO-Gluten-Free-By-Piping-Rock/2113563145 ; https://www.walmart.com/ip/BESTVITE-Berberine-500mg-120-Vegetarian-Capsules-No-Fillers-No-Stearates-Vegan-Gluten-Free-Non-GMO/191146997 ; https://www.walmart.com/ip/Dihydroberberine-Super-Berberine-Supplement-GlucoVantage-200mg-Now-5X-More-Effective-Than-Regular-HCL-Powder-Capsules-Metabolism-Support-Keto-Friendl/2212733860 ; https://www.walmart.com/ip/NTC-Dihydroberberine-200-MG-V1-60-CAP/6524505406 ; https://www.walmart.com/ip/Nutricost-Dihydroberberine-Capsules-100mg-60-Capsules-More-Bioavailable-Metabolite-of-Berberine/6524661681 ; https://www.walmart.com/ip/Nutri-Dihydroberberine-Supplement-With-Ceylon-Cinnamon-200mg-60-Capsules/15321407408 ; https://www.walmart.com/ip/Ultra-Berberine-Enhanced-Absorption-60-Capsules/15950771287 ; https://www.walmart.com/ip/WellBetX-Berberine-500-mg-by-Natural-Factors-120-Capsules/694115274
2124	https://www.amazon.com/Dihydroberberine-Supplement-200mg-Capsules-Effective/dp/B0CWC6F56X/ref=sr_1_2_sspa?th=1 ; https://www.amazon.com/product-

	reviews/B095JCB9B9/ref=cm_cr_ar_paging_btm_2?ie=UTF8 ; https://www.amazon.com/Super-Berberine-GlucoVantage%C2%AE-Berberine-Metabolism/dp/B095JCB9B9/ref=sr_1_7?dib=eyJ2IjoiMSJ9.U1S-iDsa_TH6V8xwfiXrshIUfKTC9vmOXyaCZXk-nUnlTrh8q0zrzufpTf68sFO4r9TkGDaX-jitZSwXKMnA3-b0j1_T91Y82s5zqpIdOB0zG4jDRMa_5fVsf8i1dpAYWNOGRoSlyksJ_cK1nz9-t0vW6u-eyMfgmzWJActKr8XaFXOwYbYN07jWYaj2Y8GjWTPC4zjRYmp0qt_8ZSQVrM6-De7-La4KWmWc85hJkZ6quozg2EYraIUyQOIrYiEDDUb8gq1zdHIej96ue0g6Pgm93cQHUZfukpy4Agd_IEQ.kWMsjwjfbypqHqAcUhEH-Adh4V5siBKfYreWiE3m_pU&dib_tag=se&keywords=glucovantage&q_id=1782988940&rdc=1&sr=8-7
2125	https://synapse.patsnap.com/article/bonerge-begins-human-trials-for-glucosoberC2AE-dihydroberberine-and-befisetinC2AE-fisetin
2126	Deposition of Matthew Peterson, February 26, 2026; Exhibits 7, 11, 15, 16, 18, and 19 – HIGHLY CONFIDENTIAL ATTORNEYS EYES ONLY (Filed with Motion to Seal); Redacted Version at Exh. 2148
2127	https://www.naturesfusions.com/product/nutri-dihydroberberine-supplement-with-ceylon-cinnamon-100mg-60-capsules ; https://www.naturesfusions.com/product/nutri-dihydroberberine-supplement-with-ceylon-cinnamon-200mg-60-capsules/?add-to-cart=27349 ; https://www.naturesfusions.com/product-category/supplements/
2128	1.14 VINATURA; 1.19 Pure Nootropics; 1.21 Dihydroberberine – Recalibrate Me; 1.34 Irwin Naturals; 2.7 Stacked Hydroxycut Pro; 3.20 NutraBio GDA; 3.8 Nutricost
2129	https://www.intimaterose.com/products/dihydroberberine-supplement
2130	https://www.gq.com/story/berberine-tiktok ; https://www.teenvogue.com/story/berberine-isnt-natures-ozempic ; https://nypost.com/2023/05/31/experts-warn-of-dangers-of-natures-ozempic-on-tiktok/
2131	https://clinicaltrials.gov/study/NCT07210684
2132	https://www.globenewswire.com/news-release/2023/02/20/2611285/0/en/Berberine-Supplements-

	Market-is-estimated-to-be-worth-US-2-1-Billion-by-2033-end-Exclusive-Report-by-Persistence-Market-Research.html; https://www.persistencemarketresearch.com/market-research/berberine-supplements-market.asp ; https://www.verifiedmarketresearch.com/product/berberine-supplement-market/ ; https://advancedlabsinc.com/berberine-market-to-grow-128-but-we-tested-brands-with-0-potency/ ; https://market.us/report/berberine-supplements-market/ ; https://www.factmr.com/report/berberine-supplement-market
2133	https://www.spins.com/about ; https://www.spins.com/wp-content/uploads/2023/08/2023-Mid-Year-Trends-VMS_Powering-Up-Mid-Year-VMS-Trends-Report.pdf ; https://www.spins.com/wp-content/uploads/2024/01/SPINS-2024-Trends-Predicions.pdf ; https://www.supplysidesj.com/supplements/new-data-confirms-how-tiktok-sprayed-gasoline-on-the-flame-of-berberine-sales ; https://agfundernews.com/from-glp-1-companion-foods-to-natures-ozempic-what-the-new-breed-of-weight-loss-drugs-means-for-the-food-industry
2134	https://www.cbinsights.com/company/nnb-nutrition
2135	https://www.vcbeathealth.com/entity/218476
2136	Documents NNB000008 – 14; NNB000119 – 126; NNB000127 – 130; NNB000131 – 142
2137	https://www.ccof.org/directory-member/natures-fusions-llc
2138	PDF of Gross Profit for GlucoVantage – HIGHLY CONFIDENTIAL ATTORNEYS EYES ONLY (Filed with Motion to Seal) – Native Excel file is Exh. 2178; Redacted Version at Exh. 2149
2139	https://www.exchange-rates.org/exchange-rate-history/cny-usd-2019 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2020 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2021 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2022 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2023 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2024 ; https://www.exchange-rates.org/exchange-rate-history/cny-usd-2025
2140	Documents BON01141-BON01143; BON01147; BON01151-BON01152; BON01159; BON01163; BON01167-BON01169;

	BON01171-BON01182; BON01191; BON01193; BON01195; BON01197-BON01199 – HIGHLY CONFIDENTIAL – ATTORNEYS EYES ONLY (Filed with Motion to Seal); Redacted Version at Exh. 2150
2141	https://www.uspto.gov/web/offices/pac/mpep/s2141.html ; https://www.uspto.gov/web/offices/pac/mpep/s2143.html ; https://www.uspto.gov/web/offices/pac/mpep/s716.html
2142	https://blog.priceplow.com/supplement-research/dihydroberberine ; https://blog.priceplow.com/supplement-research/dihydroberberine/glp1-weight-loss
2143	PDF of GlucoVantage SALES DATES-Till 2026.3.31 HIGHLY CONFIDENTIAL ATTORNEYS EYES ONLY (Filed with Motion to Seal) – Native Excel file is Exh. 2179; Redacted Version at Exh. 2151
2144	PDF of NNB Consolidated Income Statement 2019-2025.07 HIGHLY CONFIDENTIAL ATTORNEYS EYES ONLY (Filed with Motion to Seal) – Native Excel file is Exh. 2180; Redacted Version at Exh. 2152
2145	https://www.iherb.com/pr/best-naturals-berberine-500-mg-120-capsules/125080 ; https://www.iherb.com/pr/natural-factors-wellbetx-berberine-120-vegetarian-capsules-500-mg-per-capsule/85657 ; https://www.iherb.com/pr/nutricost-dihydroberberine-100-mg-60-capsules/143018 ; https://www.iherb.com/pr/nutri-dihydro-berberine-60-vegan-capsules/144385 ; https://www.iherb.com/pr/source-naturals-berberine-500-mg-120-vegetarian-capsules/144255 ; https://www.iherb.com/pr/toniiq-dihydro-berberine-1000-60-capsules/155891
2146	https://doublewoodsupplements.com/products/dihydroberberine ; https://www.dpsnutrition.net/i/36407/double-wood-supplements-dihydroberberine-100-mg-6.htm ; https://www.vitacost.com/products/best-naturals-berberine-500-mg-120-capsules-125080 ; https://www.vitacost.com/products/nutri-dihydro-berberine-60-vegan-capsules-144385 ; https://nutriflair.com/products/dihydroberberine-250mg-60-capsules ; https://www.vitaminshoppe.com/p/ultra-berberine-60-capsules/hfm-14610 ; https://www.naturecity.com/products/true-berberine ; https://www.xymogen.com/product/berberine-es-5-60-

	capsules; https://business.walmart.com/ip/Best-Naturals-Berberine-500mg-120-Capsules-Supports-Immune-Function-Cardiovascular-Gastrointestinal-Function/253667316 ; https://www.zotezo.com/us/reviews/natures-pure-berberine-hcl-capsules
2147	Complaint for Patent Infringement, Case No. 5:25-cv-00271, January 31, 2025 (Complaint from Parallel Litigation)
2148	REDACTED Version of Exh. 2126 – Deposition of Matthew Peterson, February 26, 2026; Exhibits 7, 11, 15, 16, 18, and 19
2149	REDACTED Version of Exh. 2138 – PDF of Gross Profit for GlucoVantage
2150	REDACTED Version of Exh. 2140 – Documents BON01141-BON01143; BON01147; BON01151-BON01152; BON01159; BON01163; BON01167-BON01169; BON01171-BON01182; BON01191; BON01193; BON01195; BON01197-BON01199
2151	REDACTED Version of Exh. 2143 – PDF of GlucoVantage SALES DATES-Till 2026.3.31
2152	REDACTED Version of Exh. 2144 – PDF of NNB Consolidated Income Statement 2019-2025.07
2153	Curriculum Vitae of Stephen Holzen
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
2165	Documents NNB 131-142
2166	A. Agarwal et al. (2025), Beyond Berberine: The Therapeutic Revolution of Dihydroberberine, Int. J. Sci. Res. Eng. Mgmt. 9(6), 1-10 DOI: 10.55041/IJSREM51151
2167	Raccah, D. et al. (2017), A global study of the unmet need for glycemic control and predictor factors among patients with type 2 diabetes mellitus who have achieved optimal fasting plasma glucose control on basal insulin, Diab. Metab. Res. Rev. 33; e2858, 1-10 https://doi.org/10.1002/dmrr.2858
2168	Peak Performance Blog, Nov. 10, 2025, Dihydroberberine Supplement: Boost Metabolic Health (https://buypeakperformance.com/blogs/blogs/dihydroberberine-supplement)
2169	Vinatura Store Website, Jan. 23, 2026, GlucoVantage®: Unlocking the True Potential of DihydroBerberine (https://www.vinatura.store/blogs/articles/what-is-glucovantage)
2170	USPTO Trademark Registration No. 7,932,736 for GLUCOSOBBER
2171	PricePlow Blog, Nov. 30, 2023, GlucoVantage Dihydroberberine Beats Berberine in Human Trial (https://blog.priceplow.com/supplement-research/dihydroberberine-vs-berberine)
2172	Fonseca, V.A. (2014), New Developments in Diabetes Management: Medications of the 21st Century, Clinical Therapeutics 36(4), 477-484
2173	Documents NF 1-21 (pages 1-3 HIGHLY CONFIDENTIAL –

	ATTORNEYS EYES ONLY (Filed with Motion to Seal)); Redacted Version at Exh. 2177
2174	Fryar, C.D. et al. (2018), Mean Body Weight, Height, Waist Circumference, and Body Mass Index Among Adults: United States, 1999–2000 Through 2015–2016, U.S. Dept. Health & Human Services, CDC, National Health Statistics Reports 122:1-16
2175	Maubon, N. et al. (2007), Analysis of drug transporter expression in human intestinal Caco-2 cells by real-time PCR, Fundamental & Clinical Pharmacology 21:659–663 doi: 10.1111/j.1472-8206.2007.00550.x
2176	Sun, D. et al. (2002), Comparison of Human Duodenum and Caco-2 Gene Expression Profiles for 12,000 Gene Sequences Tags and Correlation with Permeability of 26 Drugs, Pharmaceutical Research, 19(10), 1400-1416
2177	REDACTED Version of Exh. 2173 – Documents NF 1-21
2178	Native Excel file version of Exh. 2138 (Filed with Motion to Seal)
2179	Native Excel file version of Exh. 2143 (Filed with Motion to Seal)
2180	Native Excel file version of Exh. 2144 (Filed with Motion to Seal)
2181	Declaration of Stephen A. Holzen HIGHLY CONFIDENTIAL ATTORNEYS EYES ONLY (Filed with Motion to Seal) – Redacted Version at Exh. 2182
2182	REDACTED Version of Exh. 2181 – Declaration of Stephen A. Holzen
2183	Declaration of Dr. Louis J. DeFilippi, Ph.D.

PATENT OWNER'S RESPONSE TO PETITION

I. INTRODUCTION

Patent Owner, Nanjing Nutrabuilding Bio-Tech Co., Ltd. (“Patent Owner” or “NNB”) respectfully requests that the Board confirm the validity of claims 1, 2, 5, 6, and 7 of U.S. Patent No. 10,278,961 (the “’961 Patent”) that are the subject of Bonerge Lifescience (Hunan) Co., Ltd.’s (“Petitioner” or “Bonerger”) petition for inter partes review. For reference, Patent Owner may refer herein to the petition as “Petition,” inter partes review as “IPR,” and claims 1, 2, 5, 6, and 7 of the ‘961 Patent as the “Challenged Claims.”

Briefly, Petitioner has not shown a combination of references that discloses administration of ~25-800 mg of dihydroberberine (“dhBBR”) to humans for the purpose of managing glucose tolerance (i.e., regulating or controlling fasting glucose levels or the body’s ability to metabolize ingested glucose). Nor has Petitioner identified a combination of references where there are rational underpinnings to both combine *and* modify the references (as both combination and modification are needed here) with a reasonable expectation of success. Accordingly, the Board should uphold the validity of the Challenged Claims.

II. BACKGROUND

A. Brief Background of U.S. Patent 10,278,961

NNB owns the ‘961 Patent by assignment. Claim 1 of the ‘961 Patent reads:

A method of managing glucose tolerance in an individual, the method comprising: administering, to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.

Exh. 1001 (at p. 11).

The application for the '961 Patent commenced with the filing of U.S. Provisional Patent Application number 62/324,794, filed on April 19, 2016. Exh. 1001 (at p. 1). Non-Provisional Patent Application number 15/491,933 was filed on April 19, 2017 with a priority claim to the provisional application. *Id.* Following a restriction requirement dated December 4, 2017 and a response thereto, the Examiner issued a § 102 rejection on May 24, 2018 (Exh. 1002 at pp. 121-124), including to claim 1, which read:

A method of managing glucose tolerance in an individual, the method comprising: administering to an individual, a pharmaceutically effective amount of dihydroberberine.

Id. at p. 150.

In response to the § 102 rejection, on November 20, 2018, Applicant amended claim 1 to read:

A method of managing glucose tolerance in an individual, the method comprising: administering to an individual, a pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.

Id. at p. 116 (underline in original).

On December 26, 2018, the Examiner issued a Notice of Allowance allowing claim 1 (and its dependents). *Id.* at pp. 94-100.

The ‘961 Patent issued on May 7, 2019. Exh. 1001 (at p. 1).

III. CLAIM CONSTRUCTION

The Parties claim construction positions from the parallel litigation are set forth in Exh. 1017. Other than the construction of the “approximately ...” limitation (Exh. 1017, p. 5) wherein Petitioner argues the term is indefinite in the district court, but sufficiently understandable in this proceeding (Paper 10 at 4), the Board should utilize the proposed constructions in Exh. 1017 for purposes of this proceeding.

In an IPR, claim language is given its ordinary and customary meaning in light of the specification. 37 CFR §42.100(b). Further, claim language, to the extent it requires construction, is interpreted according to the well-known Federal Circuit

case, *Phillips v. AWH Corp.*, 415 F.3d 1303 (Fed. Cir. 2005).

Briefly, regarding the preamble¹, Petitioner admits that “managing glucose tolerance” in the preamble pertains to both fasting and postprandial glucose. *See* Paper 2 at 9 (“The ’961 patent sets forth ‘managing glucose tolerance’ to include ‘decrease and/or maintain blood glucose level, decrease and/or maintain fasting blood glucose, increase ability to process glucose, etc.’ *Id.* at **2:20-23.**”) (emphasis added). This aligns with Patent Owner’s proposed construction for the limiting preamble set forth in Exh. 1017, p. 3 (“Regulating or controlling fasting glucose levels or the body’s ability to metabolize ingested glucose”), with the following support from the ’961 Patent (including that which in bold overlaps with Petitioner’s statement in Paper 2 at 9) – ‘961 Patent (Exh. 1001) at Abstract; **Col. 2:18-23**; Col. 3:55-56; Col. 10:19-22; Claim 2.

In Paper 10, relative to Paper 2, Petitioner seems to have changed its position on how the preamble limits the claim. In Paper 10, Petitioner says the preamble should be given its plain and ordinary meaning. Paper 10 at 1. Petitioner then says that a POSITA would understand glucose tolerance in connection with a glucose tolerance test, and violates the canons of claim construction by importing limitations from the specification into the claims in requiring the claim language to be

¹ Petitioner and Patent Owner agree the preamble should be construed as limiting claim 1. Aside from the agreement, additional bases for doing so is set forth in Paper 8 at 6-7.

“measurable via a glucose tolerance test.” *MBO Laboratories, Inc. v. Becton, Dickinson & Co.*, 474 F.3d 1323 (Fed. Cir. 2007); *see also Liebel-Flarsheim Co. v. Medrad, Inc.*, 358 F.3d 898, 913 (Fed. Cir. 2004) (“it is improper to read limitations from a preferred embodiment described in the specification – even if it is the only embodiment – into the claims absent a clear indication in the intrinsic record that the patentee intended the claims to be so limited.”). There is no indication in the record that Patent Owner sought to limit the preamble to that which is measurable by a glucose tolerance test.

Furthermore, Petitioner’s proposed construction from the district court (Paper 10, p. 3 (“enhancing an individual’s ability to process glucose that is measurable via a glucose tolerance test”) is inconsistent with Petitioner’s statement at Paper 2 at 9 inasmuch as the Paper 2 at 9 version acknowledges that managing glucose tolerance included managing fasting glucose; whereas, at Paper 10, p. 3, Petitioner only seems to include managing postprandial glucose as evidenced by the word “process” in its proposed construction. Managing glucose tolerance pertains to both fasting and postprandial glucose. *See* Exh. 1001 at Abstract; Col. 2:18-23; Col. 3:55-56; Col. 10:19-22; Claim 2.

For these reasons, Petitioner’s proposed construction of how the preamble limits the claims should be rejected and Patent’s Owner’s proposed construction should be adopted.

Similarly to the preamble, Petitioner improperly imports the requirement of a glucose tolerance test into the “administering ...” limitation. For the same reasons as the preamble, there is no basis for Petitioner to have done so as there is no evidence that Patent Owner clearly sought to limit its claims in that manner.

Again, Petitioner seems to be hedging, claiming the “administering ...” limitation should be given its plain and ordinary meaning (Paper 10 at 3), but then offering a construction in the district court that imports limitations from the specification. This hedging should not be permitted.

Furthermore, as to the “administering ...” limitation, Petitioner offers a concerning statement at Paper 10 at 3 – “Third, Petition’s prior art analysis is consistent with the proposed scope in the district court litigation.” This seems to suggest that the claim construction is being influenced by Petitioner’s invalidity assertions, which is also not a canon of claim construction.

With respect to the “approximately ...” claim language, Petitioner asserts indefiniteness in the district court (Exh. 1017, p. 5), but seems to understand it well enough for this proceeding (Paper 10 at 4), although it provided no construction. As such, if a construction is needed at all, the Board should construe it as “about 25 mg to about 800 mg of dihydroberberine.” *See* Exh. 1017, p. 10-36; *see also Ferring B.V. v. Watson Labs., Inc.-Fla.*, 764 F.3d 1382, 1388 (Fed. Cir. 2014); *Merck & Co. v. Teva Pharms. USA, Inc.*, 395 F.3d 1364, 1369 (Fed. Cir. 2005); *Pall Corp. v.*

Micron Separations, Inc., 66 F.3d 1211, 1217 (Fed. Cir. 1995).

Regarding the “reduces fasting glucose levels” limitation of claim 2, Petitioner’s proposed construction should be rejected for improperly importing the glucose tolerance test element from the specification for the same reasons discussed above, wherein there is no basis to contend that Patent Owner clearly sought to limit the claim language in that manner.

From the intrinsic evidence, a POSITA would understand the phrase, “the administration of dihydroberberine reduces fasting glucose levels” to mean giving dhBBR to a person will lower glucose levels when the person had fasted for a typical period of time when glucose levels would be at rest for purposes of determining glucose levels – not a protracted, multi-day fast. *See* Exh. 1001 at Abstract; Col. 2:18-26; Col. 3:51-56; Col. 10:19-22.

Simply, a POSITA would understand that when a person goes to a doctor for an annual physical, the standard bloodwork tests for blood glucose levels, and the person is typically instructed to fast overnight before a morning test or for approximately 6-8 hours if the test is later in the day. This is a standard understanding of the general population and a POSITA.

Accordingly, if this term requires construction at all, which Patent Owner does not believe it does, the Board should refrain from adopting Petitioner’s construction that imports the glucose tolerance test into straightforward claim language.

IV. PETITIONER'S OBVIOUSNESS CHALLENGES EACH FAIL ON THE MERITS

The basis of all Petitioner's challenges in this proceeding is obviousness under 35 U.S.C. § 103. Petitioner bears the burden of proving by a preponderance of the evidence that the challenged claims were obvious before the effective filing date of the claimed invention. *In re Magnum Oil Tools International, Ltd.*, 829 F.3d 1364, 1375-76 (Fed. Cir. 2016).

A. Legal Standard for Obviousness

A claim is unpatentable as obvious under 35 U.S.C. § 103(a) if the differences between the claimed subject matter and the prior art are such that the subject matter as a whole would have been obvious before the effective filing date to a person having ordinary skill in the art to which the claimed invention pertains. *KSR Int'l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007); *see also* 35 U.S.C. § 103. Obviousness is assessed from the viewpoint of the knowledge of a person having ordinary skill in the art at the time of the invention. *Graham v. John Deere Co.*, 383 U.S. 1, 3 (1966).

1. *Graham* Factors

Obviousness is a question of law based on the following underlying factual findings: (1) the scope and content of the prior art; (2) the differences between the claims and the prior art; (3) the level of ordinary skill in the art; and (4) objective indicia of nonobviousness. *Graham*, 383 U.S. at 17-18. The obviousness inquiry

requires examination of all four *Graham* factors. *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1375 (Fed. Cir. 2012).

It is not sufficient that a challenger simply show that all elements of the claimed invention are present in the prior art; *rather*, two additional elements must be proven by a challenger: (1) motivation to combine or modify the prior art references and (2) a reasonable expectation of successfully achieving the claimed invention based on the combination or modification. *Eli Lilly & Co. v. Teva Pharms. Int'l GmbH*, 8 F.4th 1331, 1344 (Fed. Cir. 2021); *see also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 994 (Fed. Cir. 2009).

a. Scope and Content of the Prior Art

The scope and content of the prior art must be viewed from the time the invention was made to avoid impermissible hindsight. MPEP § 2141.01(III). And, “the prior art must be considered as a whole for what it teaches.” *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1166 (Fed. Cir. 2006).

For a reference to be proper for use in an obviousness rejection under 35 U.S.C. § 103, the reference must be analogous art to the claimed invention. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). 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. *Id.*; *see also Airbus S.A.S. v. Firepass Corp.*, 941 F.3d 1374, 1380 (Fed. Cir. 2019).

b. Differences Between the Claimed Invention and the Prior Art

The differences between the prior art and the claimed invention must be ascertained. *Graham*, 383 U.S. at 14. If needed, it is necessary to construe the challenged claims in order to be able to discern the differences between the prior art and claimed invention. *Abbott Laboratories v. Andrx Pharmaceuticals, Inc.*, 452 F. 3d 1331, 1336 (Fed. Cir. 2006) (“Once the scope of the claims are determined, the actual obviousness determination under 35 U.S.C. § 103 begins.”).

c. Level of Ordinary Skill in the Art

The Federal Circuit has described this element as, “the characteristics and understanding of an individual of ordinary skill in the relevant field of art at the time of invention.” *Source Search Techs., LLC v. LendingTree, LLC*, 588 F.3d 1063, 1069 (Fed. Cir. 2009). “Factors that may be considered in determining level of skill include: type of problems encountered in art; prior art solutions to those problems; rapidity with which innovations are made; sophistication of the technology; and educational level of active workers in the field.” *Mintz v. Dietz & Watson, Inc.*, 679 F. 3d 1372, 1376 (Fed. Cir. 2012).

As it pertains to both the person of ordinary skill in the art and the entire inquiry, the obviousness analysis should *not* be performed using a present-day perspective, and should *not* use hindsight. *ATD Corp. v. Lydall, Inc.*, 159 F.3d 534, 546 (Fed. Cir. 1998).

d. Motivation to Combine or Modify the Prior Art

Assuming a challenger shows all elements of the claim are present in the prior art combination or modification proposed, the question is whether a person of ordinary skill in the art would have combined elements from specific references in the way the claimed invention does (i.e., to arrive at the claims' actual limitations). *Axonics, Inc. v. Medtronic, Inc.*, 73 F.4th 950, 957-58 (Fed. Cir. 2023); *Active Video Networks, Inc. v. Verizon Communications, Inc.*, 694 F.3d 1312, 1328 (Fed. Cir. 2012). A failure to establish this element is fatal to an obviousness challenge. *Kinetic Concepts, Inc. v. Smith & Nephew, Inc.*, 688 F. 3d 1342, 1367, 1369-71 (Fed. Cir. 2012). In articulating a motivation to combine, "there must be some articulated reasoning with some rational underpinning to support the legal conclusion of obviousness." *In re Kahn*, 441 F.3d 977, 988 (Fed. Cir. 2006).

A prior art reference may teach away from a given combination of prior art and thus negate a motivation to combine or modify the prior art to meet the claimed invention. *Medichem, S.A. v. Rolabo, S.L.*, 437 F.3d 1157, 1165 (Fed. Cir. 2006). "A reference may be said to teach away when a person of ordinary skill, upon reading the reference, would be discouraged from following the path set out in the reference, or would be led in a direction divergent from the path that was taken by the applicant." *In re Kahn*, 441 F.3d at 977, 990 (Fed. Cir. 2006) (*quoting In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994)) (internal quotation marks omitted).

e. Reasonable Expectation of Success

A reasonable likelihood of success is required to establish obviousness. MPEP § 2143.02; *Amgen, Inc. v. F. Hoffman-La Roche Ltd.*, 580 F.3d 1340, 1362 (Fed. Cir. 2009). Even if a reason to combine or modify the prior art to overcome the differences between the existing art and the claimed invention, “‘the likelihood of success’ in combining or modifying prior art disclosures to meet the limitations of the claimed invention” is still required. MPEP § 2143.02 (*quoting Elekta Ltd. v. ZAP Surgical Sys., Inc.*, 81 F.4th 1368, 1375, (Fed. Cir. 2023) and *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

A “finding by the Board that a patent challenger has demonstrated a motivation to combine references does not necessarily imply that the challenger has also met its burden of showing a reasonable expectation of success in achieving a claimed method of treatment.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331 (Fed. Cir. 2021).

V. THE LEVEL OF ORDINARY SKILL IN THE ART

In light of the law cited above, Patent Owner does not believe Petitioner’s assertions regarding the level of skill in the art are correct or complete.

A POSITA during the relevant time period would likely be an individual with significant knowledge of and skill in physiology, not just chemistry or medicinal

chemistry; one who is trained to understand and interpret the various models used in the cited research studies. *See* Exh. 2108 at ¶ 30. The POSITA would likely have ~5-8 years of experience in academic research and/or industry, and that ~5-8 years may include a Master's degree or Ph.D., in the fields of diabetes research, glucose metabolism, exercise physiology (which necessarily requires an understanding of glucose metabolism), preclinical drug development, pharmaceutical sciences, translational medicine or the like. *Id.*; *see also* Exh. 2109 at ¶ 29. Furthermore, a POSITA would have a sufficient understanding of research design and basic statistics for the purpose of determining the statistical significance and relevance of data they observe. *See* Exh. 2109 at ¶ 29. A POSITA with this relevant experience would be aware that the metabolism of berberine and its derivatives involves the digestive tract and gut microbiota, which differ between from species to species. *Id.* at ¶ 30

Alternatively, Patent Owner submits that a POSITA could have a Ph.D. or equivalent degree in biochemistry, pharmaceutical sciences, physiology, translational medicine, preclinical drug development, or a related biomedical field, or a master's degree with at least 2-3 years of experience in preclinical drug development. *See* Exh. 2183, ¶¶ 40-41.

VI. THE SCOPE AND CONTENT OF THE PRIOR ART DOES NOT TEACH THE CLAIM LIMITATIONS AS REQUIRED

The scope and content of the prior art cited by the Petitioner fails to teach each and every claim limitation of each of the Challenged Claims. Claim 1 is directed to a method of “managing glucose tolerance” in an individual by administration of dhBBR at “approximately 25 mg to approximately 800 mg.” Dependent claims 2, 5, 6, and 7 disclose additional limitations including “reduc[ing] fasting glucose levels,” “orally administered as a capsule or tablet,” “orally administered as at least one of a food product or beverage product,” and “administered at least once daily.”

Patent Owner will detail immediately below the scope and content of the prior art and differences between the prior art and claimed invention in connection with each of the Grounds 1-4 put forth by Petitioner.

Based on the legal standards set forth above for obviousness, none of the cited references alone or in combination disclose each limitation of the challenged claims. Patent Owner further notes that its demonstration that claim 1 is non-obvious carries over to dependent claims 2, 5, 6, and 7.

A. Ground 1: Claims 1, 2, 5, 6, and 7 are Not Obvious in light of Turner in View of Shaw

1. Turner

Turner is entitled, “Berberine and Its More Biologically Available Derivative, Dihydroberberine, Inhibit Mitochondrial Respiratory Complex I.” Exh. 1004, p. 1. Petitioner relies heavily on Turner to show reduction of post-prandial glucose in

rodents. Paper 2 at p. 12-14. Turner, however, suffers from several substantial experimental design flaws that greatly limit its value and relevance to a POSITA and would counsel against using it as a primary reference in an obviousness challenge. *See* Exh. 2108 at ¶¶ 70, 107; Exh. 2183 at ¶¶ 164-173.

First, Turner utilized intraperitoneal administration of glucose, which is physiologically irrelevant in the context of humans, and which does not yield the same results as oral ingestion of glucose. *See* Exh. 2108 at ¶¶ 46 (discussing Bowe, which is Exh. 2094, p. 4-5 therein), 48, 66, 72; Exh. 2183 at ¶¶ 46, 66, 67, 82.

Second, Turner utilized an overnight fast (*see* Exh. 1004, p. 2 – under “Animals” and “In vivo glucose metabolism,” citing reference 10 (Molero – Exh. 2105)). The overnight fast of the mice will produce a stress response that was not controlled for by Turner, and that results in a state in the mice akin to starvation. *See* Exh. 2108 at ¶ 74 (citing Exhs. 2094, p. 3 and 2102, pp. 2-3); Exh. 2109 at ¶ 54.

Third, in his in vivo glucose metabolism experiments, Turner used anesthesia that was known to cause perturbations in glucose metabolism. (*see* Exh. 1004, p. 2 – under “In vivo glucose metabolism” citing reference 9 (Ye – Exh. 2103)); *see also* Exh. 2108 at ¶ 75 (citing Exh. 2104 (Saha), pp. 1, 7). Patent Owner’s declarant, Dr. Kerksick², noted that the anesthesia used by Turner:

² As previously indicated, Dr. Kerksick is a scientific advisory board member for Patent Owner. *See* Paper 8 at 50; Exh. 2108 at ¶ 5.

would have completely altered the regulation of glucose and insulin throughout the glucose tolerance tests completed by Turner. By using an incorrect anesthetic and not controlling for it in any way, the results in Turner are compromised and its gratuitous speculation about possible human benefit is not based on any data, but rather unwarranted speculation. In my opinion, unprovoked speculation, particularly where the experiments were so poorly designed given the physiological system under investigation, does not make a researcher or clinician even curious, let alone motivated to investigate further. In my opinion, Turner is useless in the obviousness argument of Petitioner.

Exh. 2108 at ¶ 75.

The foregoing severely limits, if not completely guts, Turner's utility as a reference for establishing obviousness for managing glucose tolerance with dhBBR in humans. *See* Exh. 2108 at ¶¶ 70, 92, 107; Exh. 2183 at ¶¶ .

Other experimental design disconnects between Turner's experimental subjects (rodents, mitochondria, L6 myotubes) and living humans further compromise Petitioner's assertion that a POSITA would have a reasonable

expectation of success combining Turner with any of the other references relied upon by Petitioner, and then further modifying the combination (because none of the proposed combinations themselves teach each and every limitation of the Challenged Claims – modification is also required). *See* Exh. 2183 at ¶¶ 48, 52-65, 67-74, 80-83.

In addition to the foregoing deficiencies in Turner, and contrary to Petitioner’s generalized assertions at Paper 2, pp. 26, 29 (relying on Exh. 1003, ¶ 39) and Paper 2, pp. 33 (relying on Exh. 1003, ¶ 59) that Turner teaches that dhBBR is effective for “managing glucose tolerance in rodents,” Turner does *not* teach anything regarding *fasting* blood glucose. If anything, at the zero time point in Fig. 3B, the HFD+dhBBR is *higher* than HFD alone, which shows that dhBBR *increased* fasting glucose levels, and which teaches away from dhBBR reducing fasting blood glucose levels. It certainly does not teach that dhBBR reduces *fasting* blood glucose. This is fatal to Petitioner’s reliance on Turner with respect to all of the Challenged Claims because the limiting preamble of claim 1 should be construed to pertain to glucose levels in both fasting *and* postprandial states, including where claim 2 limits the claim to specifically a fasting state; and, whereas, Turner does not address *fasting* glucose levels at all, let alone showing a reduction by dhBBR.

2. Shaw

Petitioner undiscerningly reads Shaw (Exh. 1005), especially in light of the

FDA Guidance (Exh. 1008) Shaw relies upon, which leads to Petitioner mischaracterizing what Shaw and the FDA Guidance actually teach. Additional prior art agrees with this assessment and severely criticizes Shaw to the point that the additional prior art teaches away from use of Shaw in the manner Petitioner used Shaw (and the FDA Guidance (Exh. 1008)).

In 2015, Blanchard and Smoliga recognized that “the recommendations presented by Reagan-Shaw et al. are **inappropriate**.” *See* Exh. 2157 at p. 2 (emphasis added). Blanchard-Smoliga stated that,

the 2008 paper by Reagan-Shaw et al. (3) that advocates for body surface area (BSA) scaling between species has emerged as a reference for developing human equivalent dosages from laboratory animal model experiments. The authors cite multiple references, including the U.S. Food and Drug Administration (FDA) guidelines, in an attempt to support their argument that drug dosages can be converted between species using a simple BSA conversion equation (3, 4). Although the paper has been cited >1000 times across a variety of disciplines over a 5-year span, investigation into the underlying science and interpretation of references behind the authors’ arguments

reveal major issues that severely limit the applicability of the recommendations and should cause major concern to researchers and clinicians.

Id. at p. 1.

Regarding Shaw, Blanchard and Smoliga continue:

As [Shaw] continues, these recommendations inappropriately evolve into the argument that clinically effective therapeutic doses can be derived from animal model studies simply through a BSA conversion formula, with many references cited grossly out of context (4–8). This overly simplistic conversion neglects discussion of interspecies differences in drug absorbance, metabolism, clearance, etc. These differences in pharmacokinetics greatly affect the resulting peak plasma concentration (C_{max}) values and exposure derived from area under curve (AUC), which influence the dose-response relationship of potential therapeutics (1, 2). ... Through presenting the history of BSA scaling, reviewing the literature that discredits this method, clarifying the FDA's recommendations on this issue, and using examples in

which BSA scaling could have negative consequences, **we aim to demonstrate why the recommendations presented by Reagan-Shaw et al. are inappropriate.**

Id. at p. 1-2 (emphasis added).

Regarding the updated FDA guidelines relied upon by Petitioner (*see* Exh. 1008), Blanchard and Smoliga note:

This is further clarified in the updated version of the FDA guidelines for safe starting dosages in humans from 2005 (29). It is clear that HED and PAD are 2 distinct dosages that are not interchangeable, and thus, BSA conversion is only applicable to HED. The FDA does not recommend a method to derive a PAD from model species, nor does the FDA state that scaling by BSA is the “only” method to scale for first-in-human trials (4, 31).

Id. at p. 2. Dr. Hartung, Patent Owner’s expert, concurs with Blanchard-Smoliga. *See* Exh. 2107 at ¶¶ 64, 68 (“Dose Translation” row – “BSA Scaling is intended for estimating safe starting doses (MRSD), not for predicting clinical efficacy or bioavailability.”). Dr. DeFilippi, Patent Owner’s medicinal chemistry expert, also concurs with Blanchard-Smoliga. *See* Exh. 2183 at ¶¶ 88-91.

The 2005 FDA guidelines submitted by Petitioner as Exh. 1008, and relied

upon by Petitioner, expressly state that:

Selection of a PAD 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.”

Exh. 1008, p. 15; *see also* Exh. 2107 at ¶ 64.

Therefore, the FDA guidelines followed by Shaw are *irrelevant* to the question of a pharmacologically active dose (PAD), and they cannot be relied upon to make out a prima facie case of obviousness.

The *irrelevance* of Shaw as to the use of the BSA conversion in the FDA guidelines to establish a human equivalent *pharmacologically active dose* is reinforced by the very strong criticism of the use of Shaw “to justify BSA conversion as a method to translate the pharmacologically active dosage of drugs from animals to humans” notwithstanding the fact that it “lacks scientific support. *See* Exh. 2157 at p. 4.

This criticism is further buttressed by Blanchard and Smoliga’s statement that, the use of BSA scaling is based on antiquated ideas that have been discredited and therefore is rarely justified in modern science. Contrary to the paper’s claim, the FDA does not advocate BSA or any specific method for

determining therapeutic dosage range in humans. Many of the citations of Reagan-Shaw et al. are flawed or are not applicable to interspecies scaling and ultimately do not support the claims of the authors. It 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.

Id. at p. 4-5.

Petitioner's expert, Dr. Shebuski stated that, "Shaw discloses that the BSA normalization method is the "most appropriate" method to translate drug dosage from animals to humans." *See* Exh. 1003 at ¶ 48. Dr. Shebuski falls for Shaw's overgeneralization and acknowledges, but ignores, *without justification*, the FDA's direct admonition that a pharmacologically active dose is "outside the scope of the guidance." *Id.* at ¶ 55. Therefore, Dr. Shebuski's assertions regarding Shaw and the FDA guidelines should be rejected.

A POSITA would conclude that Blanchard-Smoliga *strongly* discourages

others from following the direction advocated by Shaw in terms of using a BSA conversion to estimate a human equivalent *pharmacologically active dose* from animal data. *See* Exh. 2183 at ¶ 88. Thus, the prior art teaches away from the approach advocated by Shaw; and, the FDA guidelines explicitly disclaim any relevance of use of the BSA conversion for establishing a pharmacologically active dose as “beyond the scope of this guidance.” *See* Exh. 1008 at p. 15.

Petitioner’s argument stating the following is thus misplaced:

As explained in Shaw, the body surface area (BSA) normalization method is the “most appropriate” method to translate drug doses from animal studies to human studies. EX1005 at 661. Using BSA method for converting drug doses from animal studies to clinical trials is well known by a POSA as it is also recommended by the FDA Guideline document [footnote omitted].

Paper 2 at 22.

Petitioner claims a reasonable expectation of success in terms of the dosage of dhBBR based on use of the flawed BSA calculation. Paper 2 at 25 (1st full ¶). Again, the BSA conversion is not for determining a *pharmacologically active dose*, but a maximum safe starting dose for human trials. *See* Paper 8 at 22-23, 29-30; Exh. 2107 at ¶¶ 64, 68; Exh. 2183 at ¶¶ 90, 91, 148. Dr. Shebuski did not read the

prior art as a whole, as he is required to do (*W.L. Gore & Assoc., Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1551 (Fed. Cir. 1983)). His failure to do so led him to do what the FDA Guidance expressly taught away from, and to rely on a reference (Shaw) that itself relied on the FDA Guidance in ways *not* intended. Petitioner and Dr. Shebuski's reliance on Shaw and the FDA Guidance to establish an active or effective dose is *not* what the prior art teaches. *Chemours Company FC, LLC v. Daikin Industries, Ltd.*, 4 F.4th 1370, 1376 (Fed. Cir. 2021) ("Here, the Board appears to have ignored the express disclosure in Kaulbach that teaches away from the claimed invention and relied on teachings from other references that were not concerned with the particular problems Kaulbach sought to solve.").

Petitioner relied on Shaw/FDA in its Invalidity Chart for Claim 1 under Ground 1 in connection with the "administering, to an individual ... approximately 25 mg to approximately 800 mg of dihydroberberine." Paper 2 at p. 28-32. For the reasons already stated, Petitioner's reliance on Shaw (and the FDA guidelines) is misguided (and likely the result of hindsight bias) with the result that Petitioner's obviousness arguments in Ground 1 fail because Shaw and the FDA Guidance do not support its position.

3. Additional References Included by Petitioner in Ground 1

Without identifying them *per se* in the combination of references for Ground 1, Petitioner cites several additional references in its claim charts for Ground 1.

Patent Owner addresses the nature of the references, the differences between the references and the claimed invention, and the deficiencies in the additional references.

a. Chen

Petitioner supplements its obviousness combination in Ground 1 (Paper No. 2 at 30, 37) with Chen (Exh. 1009). To support an obviousness rejection under 35 U.S.C. § 103, a reference must qualify as analogous art. *In re Bigio*, 381 F.3d 1320, 1325 (Fed. Cir. 2004). Chen is not analogous art.

Petitioners rely on Chen to argue that “researchers in the berberine field already relied on rodent studies to launch clinical studies that yielded successes.” Paper No. 2 at 21. Chen is entitled “A randomized clinical trial of **berberine** hydrochloride in patients with **diarrhea-predominant irritable bowel syndrome**.” Exh. 1009 (emphasis added). Petitioner argues that Chen’s success in applying animal data provides a POSITA a motivation to combine Turner and Shaw. Chen, however, has nothing to do with glucose metabolism and is not analogous art because irritable bowel syndrome/diarrhea is not pertinent to the particular problem of the ‘961 Patent, managing blood sugar.

Dr. Shebuski overreads Chen by claiming that Chen teaches that “[r]esearchers in the berberine field already relied on rodent studies to launch clinical studies that yield successes.” Exh. 1003 at ¶ 47. That is not a meaningful teaching

of Chen. In fact, Chen states that, “For centuries, berberine has been used to treat diarrhea and gastroenteritis in East Asian countries because of its antimicrobial, antimotility, anti-permeability and antisecretory properties.” *See* Exh. 1009, p. 5. In other words, a POSITA, knowing that there were allegedly successful rodent studies with berberine in connection with gastrointestinal issues, would not have been motivated to see if such results were reproducible in humans, because humans had, according to Chen, been using berberine to treat diarrhea and gastroenteritis “[f]or centuries.” And, this has nothing to do with glucose metabolism.

Dr. Shebuski’s claim that Chen would have motivated the administration of dhBBR to humans *for managing glucose tolerance* is a bridge too far. *See* Exh. 1003 at ¶ 64. Chen was a *berberine* study that did not once mention dhBBR or glucose; and its focus on an unrelated condition (irritable bowel syndrome/diarrhea) makes it further irrelevant and non-motivating. *See* Exh. 2183 at ¶ 144.

Further, Chen does not provide any reasonable expectation of success for an unrelated condition (irritable bowel syndrome vs. glucose regulation). That is like saying because acetaminophen works for headaches, it provides a reasonable expectation that it also would be efficacious for the treatment of asthma.

Dr. Kerksick also noted the *irrelevance* of the Chen reference (Exh. 1009), which looked reported an effect of BBR, not dhBBR, on irritable bowel syndrome, not glucose regulation. *See* Exh. 2108 at ¶¶ 85, 86, 95. Thus, it would not motivate

any combination or provide a reasonable expectation of success on an entirely different physiological system.

b. Liu

Petitioner references Liu in its claim chart for claim 1 under Ground 1. Paper 2 at 31. Petitioner also references Liu at page 23 of Paper 2, and admits that the 200 mg/kg berberine (*not* dhBBR) dosage, when converted using the flawed Shaw/BSA calculation, produces a human concentration of 972 mg/day that is outside the range stated in claim 1 of the '961 Patent (~25-800 mg). Petitioner, reliant on Dr. Shebuski (*see* Exh. 1003 ¶ 52), however, disregards this difference from the claim language and states, “Because the HED dosage converted from the Liu rodent studies (972 mg/day) **approximates** the pharmaceutically effective BBR dosage disclosed in the Zhang clinical studies (1000 mg/day), a POSA would have understood that the BSA normalization method is validated for diabetic research on the therapeutic effects of berberine (or its derivative).” Paper 2 at 23-24 (emphasis added). No basis is given to indicate how or why a drug dosage that substantially exceeds the maximum dose in claim 1 “approximates” anything in claim 1. And, the fact that it approximates Zhang, the dose of which exceeds claim 1 by 25%, is similarly irrelevant. This is a quintessential example of improper hindsight bias.

In addition to the dosages being outside the range in claim 1, Petitioner added further gloss to say that the results of Zhang and Liu combined somehow validate a

study on the therapeutic effects of “berberine (or its derivative)” on diabetic research, even though neither Zhang, nor Liu, utilized dhBBR³, or even mentioned it, in their studies. This goes too far and is unsupported, hindsight speculation from Petitioner and Dr. Shebuski. Their commentary does not support a motive to combine or a reasonable expectation of success.

Dr. Kerksick likewise noted the *irrelevance* of the Liu reference (Exh. 1010) because its dosages were outside the range of the ‘961 Patent once extrapolated to a 60 kg human using Petitioner’s preferred method from Shaw. *See* Exh. 2108 at ¶¶ 87, 95-96. Thus, to the extent Petitioner relied upon Liu, it is not relevant to obviousness.

c. King

Petitioner cites King on page 20 of Paper 2 to assert that animal models for diabetes existed prior to the critical date for the ‘961 Patent. This is not a remarkable assertion. King, however, does not reference berberine or dhBBR. So, it is unclear how it would speak to any motivation to combine, reasonable expectation of success, or lack thereof with dhBBR. This again is hindsight reconstruction by Petitioner.

Petitioner also cites to King in its claim chart for claim 1 under Ground 1 (Paper 2 at 30) to assert that a POSITA would have been motivated to administer

³ The presumed “derivative” referenced by Petitioner at Paper 2 at 24, and by Dr. Shebuski at Exh. 1003 ¶ 52.

dhBBR to humans for managing glucose tolerance with reasonable expectation of success. Again, it is unclear how Petitioner reaches this conclusion inasmuch as King does not even mention berberine or dhBBR at all, and Petitioner offers no explanation other than asserting that King described commonly used animal models for diabetes. *See* Exh. 2183 at ¶¶ 135-141.

4. Claim Charts for Ground 1

In addition to the foregoing discussion of the prior art and its deficiencies as to Petitioner's obviousness challenge, Patent Owner notes the following additional differences between the prior art and claimed invention. To the extent Petitioner introduces additional prior art (King, Chen, Liu, FDA) into its own claim charts, Patent Owner has commented on their respective issues above, and notes that they do not support Petitioner's obviousness position.

Claim 1:

A method of managing glucose tolerance in an individual, the method comprising:	Neither Turner (Exh. 1004) nor Shaw (Exh. 1005) teach a method of managing glucose tolerance (“regulating or controlling fasting glucose levels or the body’s ability to metabolize ingested glucose” – <i>see</i> Patent Owner’s proposed construction for this limitation in Part III, <i>supra</i> ; Exh. 1003 at ¶ 29) in an individual (a “human”) – <i>see</i> Paper 2 at pp. 4 (“for
---	---

	managing human blood glucose levels” (emphasis added)), 29-30 (discussion of conversion of the pharmaceutically effective rodent dosage amount disclosed in Turner to pharmaceutically effective human dosage), which necessarily means that a human dosage was not provided by Turner. <i>See</i> Exh. 2108 at ¶¶ 48, 65, 100. Turner does not provide data regarding regulating or controlling fasting blood glucose levels in humans or otherwise with dhBBR. <i>See</i> Exh. 1004, generally; <i>see also</i> Claim Chart for Ground 1 – Claim 2, <i>infra</i>, starting with “Furthermore.” Shaw does not mention BBR, dhBBR, or glucose at all. <i>See</i> Exh. 1005, generally. And, as discussed in Part VI.A.2, <i>supra</i>, Shaw’s application of the BSA calculation to identify a human <i>effective</i> dose is improper. Blanchard and Smoliga (Exh. 2157) strongly teach away from using Shaw in this manner.
--	---

	Furthermore, to the extent the FDA Guidance (Exh. 1008) is asserted by Petitioner to support Shaw using the BSA calculation to identify a human <i>effective</i> dose, Patent Owner begs to differ. The FDA Guidance expressly states that “[s]election 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.” <i>See</i> Exh. 1008 at p. 15 (Part VIII). Based on the foregoing, the combination of Turner and Shaw does not teach a method of regulating or controlling fasting glucose levels or the body’s ability to metabolize ingested glucose in a human, as set forth in the preamble.
administering, to an individual, a	As noted immediately above, Turner did not administer dhBBR to a human at all. <i>See</i> Exh. 1004,

pharmaceutically effective amount of dihydroberberine, wherein the pharmaceutically effective amount of dihydroberberine comprises approximately 25 mg to approximately 800 mg of dihydroberberine.	generally. Turner did not provide any data that the amount of dhBBR it administered to rats (972 mg/day), which is well above of the dosage range of the claim, or mice (486 mg/day) – <i>See</i> Exh. 2108 at ¶ 64 – were or would be pharmaceutically effective in humans. Again, Shaw does not mention BBR, dhBBR, or glucose at all. <i>See</i> Exh. 1005, generally. And, as discussed in Part VI.A.2, <i>supra</i>, Shaw’s application of the BSA calculation to identify a human <i>effective</i> dose is improper. Blanchard and Smoliga (Exh. 2157) strongly teach away from using Shaw in this manner. And, again, to the extent the FDA Guidance (Exh. 1008) is asserted by Petitioner to support Shaw using the BSA calculation to identify a human <i>effective</i> dose, Patent Owner begs to differ. The FDA
---	---

	Guidance expressly states that “[s]election 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.” <i>See</i> Exh. 1008 at p. 15 (Part VIII). Based on the foregoing, the combination of Turner and Shaw does not teach administering to a human a pharmaceutically effective amount of dhBBR between ~25-800 mg.
--	--

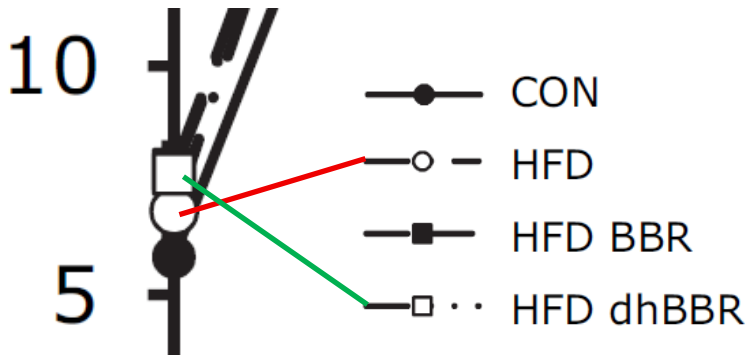
Claims 2, 5, 6, and 7:

Claim 2	
The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels.	Independent claim 1 has already been shown to be nonobvious. For the same reasons, dependent claim 2 is also nonobvious. <i>Securitypoint Holdings, Inc. v. U.S.</i>, 129 Fed.Cl. 25, 39 (Fed. Cl. 2016) (citing <i>Hartness Int’l, Inc. v. Simplimatic Eng’g Co.</i>, 819 F.2d 1100, 1108 (Fed. Cir. 1987) (a dependent claim

	is not obvious when the independent claim that it incorporates is not obvious)).⁴ Even so, the cited prior art does not provide any data regarding the impact of dhBBR on glucose regulation or fasting glucose levels in humans. <i>See</i> Exh. 2108 at ¶ 105 (“None of the studies provided by Petitioner tell us anything about how dhBBR impacts glucose regulation <i>in humans</i>.”); Exh. 2183 at ¶¶ 100, 131, 133. Furthermore, Turner does not provide data regarding regulating or controlling <i>fasting</i> blood glucose levels in humans or otherwise with dhBBR. <i>See</i> Exh. 1004, generally, including Figs. 3B and 3C. For Dr. Shebuski to suggest otherwise in ¶¶ 39, 59 of his declaration (Exh. 1003) appears to be based on a misreading of the data. Turner did not look at the
--	---

⁴ This point of law applies to the challenged dependent claims 2, 5, 6, and 7 throughout Grounds 1-4 and by this reference the same point is intended to be made by Patent Owner as to each of the dependent claims challenged in Grounds 1-4.

	effect of dhBBR on <i>fasting</i> glucose levels (let alone in humans). Figs. 3B and 3C in Turner (Exh. 1004) show glucose levels over time in a glucose tolerance test, not at rest. And, Dr. Shebuski's statement that, "The blood glucose levels of mice fed with the HFD/dhBBR diet at a 100 mg/kg/day dosage is closer to the fasting blood glucose levels of the control animals that were not fed a high fat diet" is neither here nor there because the question for claim 2 is not the effect in response to ingested glucose, but the effect while fasting. This is not shown in Turner, and whether or not the ingested data is "closer to the fasting blood glucose levels" is irrelevant to the actual effect on fasting blood glucose. And, if the zero time point in Fig. 3B of Turner is considered as a representation of the effect of berberine or dhBBR on fasting glucose levels, one would expect the "HFD dhBBR" data point to be
--	--

	<i>lower</i> than “HFD” alone if dhBBR reduced fasting glucose, but Fig. 3B shows otherwise, contradicting Dr. Shebuski’s assertion, and rebutting the notion that Turner teaches a reduction in fasting glucose levels by dhBBR:  Thus, the combination of Turner and Shaw fails to teach each and every limitation of claim 2.
Claim 5	
The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Animal chow is not a capsule or tablet, but is essentially a continuous source of food (with or without dhBBR in it) to the rat or mouse in Turner. <i>See</i> Exh. 2108 at ¶¶ 108, 112; Exh. 2109 at ¶ 56; Exh. 2183 at ¶ 191; Exh. 1004 at p. 2 (“BBR and

	dhBBR were provided in the HFD at a dose of [100 mg/kg/day] for the final 2 weeks of feeding.”). While Shaw mentions a “pill or capsule form,” it does so in reference to resveratrol, not BBR, dhBBR, or the like. Again, Shaw does not mention BBR, dhBBR, or glucose at all. <i>See</i> Exh. 1005, generally. Accordingly, the combination of Turner and Shaw does not teach all of the limitations of claim 5.
Claim 6	
The method of claim 1 wherein the dihydroberberine is orally administered as at least one of a food product or beverage product.	Turner teaches the addition of dhBBR onto animal chow, not the creation of a “food product” or “beverage product” that inherently contains the dhBBR. <i>See</i> Exh. 1004, p. 2 (under “Animals”). Shaw does not teach a food or beverage product for the compound of interest. Thus, the limitations added by claim 6 are not met.

Claim 7	
The method of claim 1 wherein the dihydroberberine is administered at least once daily.	Animal chow, as provided in Turner (<i>see</i> Exh. 1004, p. 2 – under “Animals”), is essentially continuous, not once per day. Exh. 2183 at ¶ 191. Shaw (Exh. 1005) does not speak to dosing regularity per se. Accordingly, Turner and Shaw combined do not meet the limitations of claim 7.

B. Ground 2: Claim 5 is Not Obvious in light of Turner in View of Shaw and Further in View of Zhang

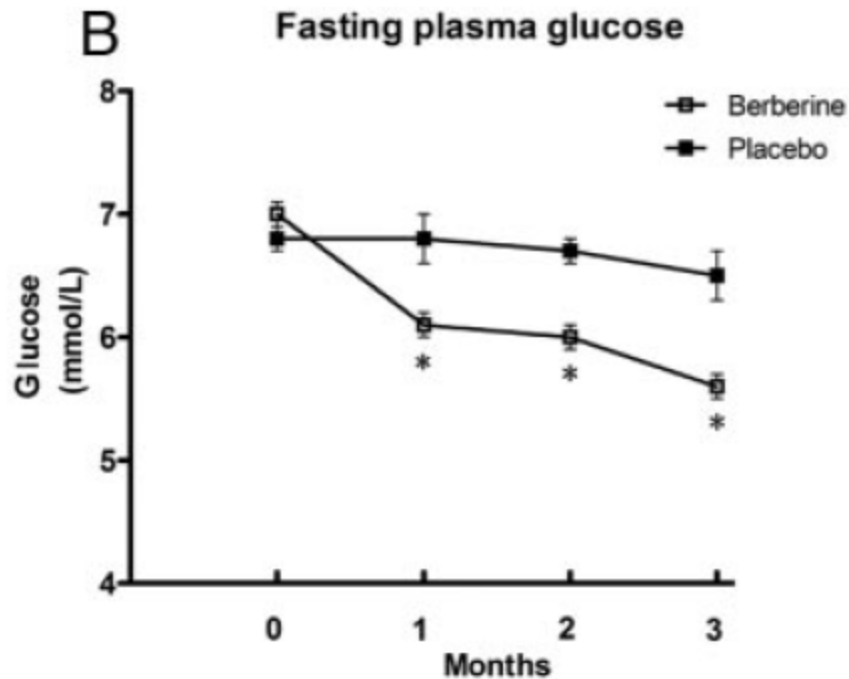
In addition to the deficiencies in the Turner-Shaw combination already noted above, what follows describes the additional Zhang reference and further explains why Petitioner’s Ground 2 arguments are unpersuasive.

1. Zhang Reference (also applicable to Grounds 3, 4)

Zhang is entitled “Treatment of Type 2 Diabetes and Dyslipidemia with the Natural Plant Alkaloid Berberine.” Exh. 1006, p. 1. Zhang does not mention dhBBR at all. Berberine and dhBBR are not the same and physiological differences between rodents and humans limit translatability of Zhang’s conclusions from rodents to

humans, including, for example, differences in gastric pH that would alter berberine to dhBBR conversion in the gut (*see* Exh. 2109 at ¶ 61 and references cited therein), intestinal glucose absorption differences (*Id.* at ¶ 63), as well as other differences noted by Dr. Tong (*Id.* at ¶¶ 67, 69). Patent Owner's experts concluded that the combination of Zhang and Feng does not render any of the Challenged Claims obvious. *See* Exh. 2107 at ¶ 59; Exh. 2108 at ¶¶ 89, 99. Exh. 2109 at ¶ 70; Exh. 2183 at ¶¶ 199-248.

In addition to the foregoing, Petitioner relies heavily on Zhang (Exh. 1006) in its Ground 3 obviousness contentions, *infra*. At Paper 2, p. 43, Petitioner cites Zhang for the proposition that diabetic patients treated with berberine (not dhBBR) 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:



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

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 the data:

2562 Zhang et al. Berberine and Antihyperglycemia and Antidyslipidemia

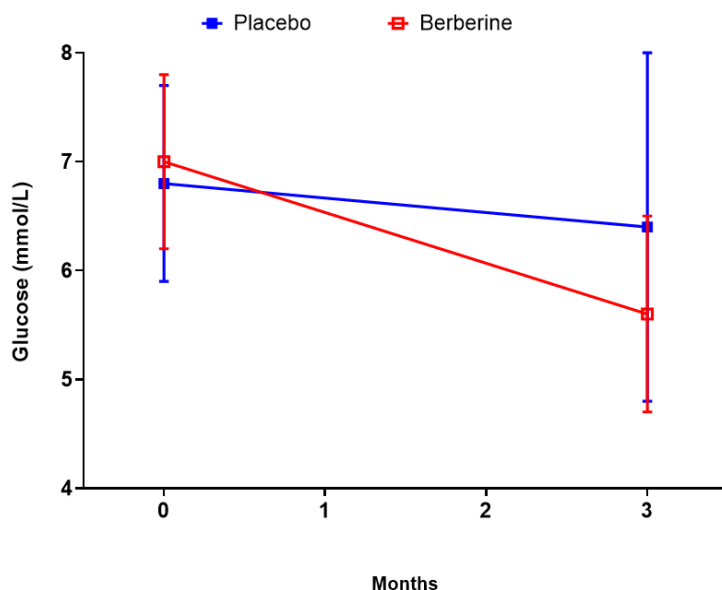
J Clin Endocrinol Metab, July 2008, 93(7):2559–2565

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

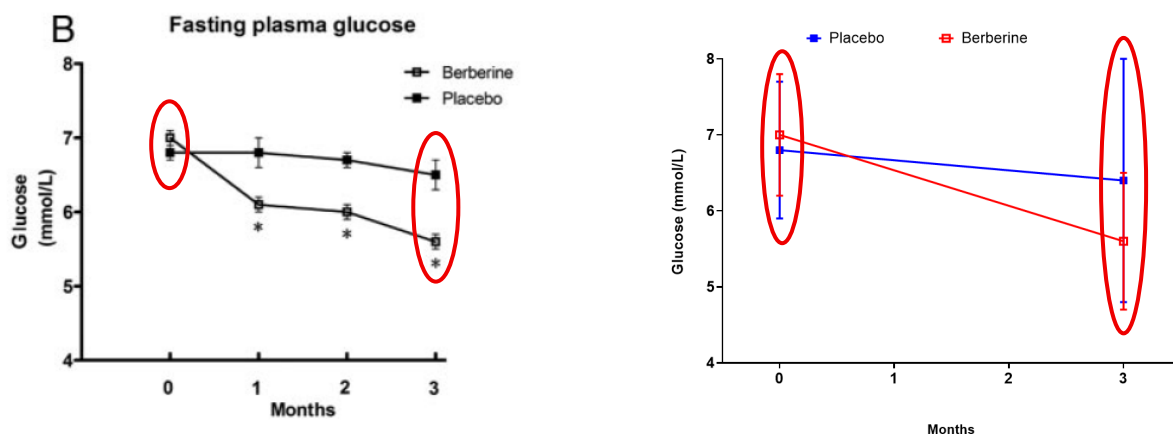
	Berberine			Placebo ^a			P value ^a
	Before	After	P value ^b	Before	After	P value ^b	
No. (male/female)		58 (30/28)			52 (31/21)		
Age (yr)	51 ± 9	51 ± 10					
Current smokers		14			20		
Alcohol use		4			15		
Body weight (kg)	68.7 ± 11.3	66.4 ± 11.8	0.000	71.8 ± 11.2	70.5 ± 11.0	0.000	0.034
BMI (kg/m 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

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

While the one (1) and two (2) month data is 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:



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



And based on this data representation irregularity, Patent Owner is highly skeptical of the claim for Fig. 3B that the statistical significance is at the $p < .0001$

level (*see* Exh. 2183 at ¶¶ 152-154):

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 ± se. *, $P < 0.0001$ after 1, 2, or 3 months treatment vs. before treatment within each group.

Exh. 1006, p. 5 (Fig. 3) (highlighting added).

Thus, Patent Owner is highly skeptical of the veracity Zhang's data, and respectfully submits 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 quickly upon reading of the article.

Petitioner and its expert, Dr. Shebuski, rely on Zhang in connection with its obviousness contentions in Grounds 3 and 4, to attempt to establish both the meeting of the limitations of claims 1 and 2 of the '961 Patent (the preamble and administration of dhBBR limitations in claim 1, and dhBBR reducing fasting glucose levels in claim 2), in particular (but also claim 6), and a motivation to combine Zhang with Feng with a reasonable expectation of success in so combining the references. *See* 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, as well as other issues noted by Dr. DeFilippi (*see* Exh. 2183 at ¶¶ 154, 221-231) a POSITA would not have relied on Zhang at all, nor combined it with Feng with any reasonable expectation of success.

2. Claim Chart for Ground 2

Claim 5:

The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Turner teaches that BBR and dhBBR were provided in the high-fat diet, which is a continuous source of food/drug, not as a standalone capsule or tablet. <i>See</i> Exh. 2109 at ¶¶ 55, 56 59; Exh. 2183 ¶¶ 196-198. Zhang does not warrant a different conclusion. Zhang does not teach the oral administration of dhBBR in a capsule or tablet. <i>See</i> Exh. 1006, generally (no references to “dihydroberberine” at all); Exh. 2109 at ¶ 59. Accordingly, Zhang does not render claim 5 obvious when considered with Turner in view of Shaw.
---	---

C. Ground 3: Claims 1, 2, 5, and 7 are Not Obvious in light of Zhang in View of Feng

1. Zhang:

Zhang is fully described above in connection with Ground 2 and that description is fully applicable to Ground 3, and is incorporated herein by reference.

2. Feng

Feng is entitled “Transforming berberine into its intestine-absorbable form by the gut microbiota.” Exh. 1007, p. 1. Feng used rodents, a cell line, and human intestinal microsomes to demonstrate that berberine is apparently reduced to dhBBR in those systems under lab conditions. *Id.* This is immaterial to Patent Owner’s invention. *See* Exh. 2107 at ¶¶ 7 (“We are not 70kg rats”), 31 (“Before 2016 ... it was well-established and widely recognized that glucose metabolism, mitochondrial complex-I responses, and intestinal transformation of xenobiotics differ profoundly between rodents and humans.”); Exh. 2108 at ¶¶ 77, 80, 84; Exh. 2183 at ¶ 211, 227-228, 233, 240.

No evidence, however, was shown in Feng to indicate that the same conversion takes place in a 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. *See* Exh. 2107 at ¶¶ 37, 47, 50 (and references cited therein), 54 (and references cited therein), 55 (and references cited therein), 63; Exh. 2108 at ¶¶ 32-40, 83.

Feng also used a dhBBR dosage in rats that when the BSA calculation that Petitioner relied on is applied, the human equivalent dose well exceeds the high end of the claimed range to the extent that it is not “approximately 800 mg.” *See* Exh. 2108 at ¶ 78. And, this is for a 60kg human, which similarly should no longer be

the standard per the CDC. *See* Exh. 2174 at p. 5 (Table 1 therein) (noting mean weights of men and women over age 20 in the U.S. in 2015-2016 to be ~90 kg and ~77 kg, respectively).⁵ And, if that were not enough, Dr. DeFilippi opined that the absorption rate claim by Dr. Shebuski in ¶ 81 of his declaration is not a sufficient predictor of human dosing anyways. *See* Exh. 2183 at ¶¶ 218-219, 225.

Additional issues exists with the data in Figs. 3(b)-3(d) in Feng that would discourage a POSITA from following such results. *See* Exh. 2108 at ¶ 79. For these and other reasons set forth in the claim charts, Feng does not support a finding that the Challenged Claims are obvious.

3. Claim Charts for Ground 3

Claim 1:

A method of managing glucose tolerance in an individual, the method comprising:	Zheng considered both fasting and postload glucose in response to berberine, not dhBBR. <i>See</i> Exh. 1006 at p. 1. Feng did not provide any data from whole-bodied humans. <i>See</i> Exh. 1007, generally; Exh. 2108 at ¶¶ 76, 77, 92; Exh. 2183 at ¶ 211, 218-219, 225, 228,
---	---

⁵ This CDC data presents yet another reason why the Shaw/FDA Guidance for the BSA conversion for safe starting doses is irrelevant – it relies on 60 kg humans! *See* Exh. 1005 at p. 2/Table 1; Exh. 1008 at p. 10/Table 1 (note a).

	233, 240.
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.	Zhang did not administer dhBBR. <i>See</i> Exh. 1006, generally. Zhang does not use the word “dihydroberberine” at all. <i>Id.</i> Zhang did not administer ~25-800 mg of dhBBR (or even berberine), but rather, administered 1000 mg of berberine (<i>see</i> Exh. 1006 at p. 2 (under “Treatment”)), which is well outside the claimed range. Dr. Shebuski’s assertion that a “POSA is motivated to find a more bioavailable derivative of BBR for diabetes treatment (<i>see</i> Paper 2, p. 54; Exh. 1003 at ¶ 83) is pure and improper hindsight. Feng administered dhBBR, but at a concentration of 200 mg/kg/day in rats (<i>see</i> Exh. 1007 at Fig. 3 and its description), which, even according to the inapplicable BSA conversion calculation from Shaw, results in a human equivalent dosage of 1945.9 mg for a 60 kg person, which is well outside the range

	set forth in claim 1 (<i>see</i> Exh. 2108 at ¶ 78). Petitioner's (<i>see</i> Paper 2 at 51-55) and Dr. Shebuski's (<i>see</i> Exh. 1003 at ¶¶ 78-90) attempts to massage the dhBBR concentrations (i.e., derive lower dhBBR concentrations from the berberine concentrations used) to come within the claimed range does not hold up because Feng used dhBBR at a human equivalent dosage 2.43-fold higher than the upper limit of claim 1. <i>See</i> Exh. 2108 at ¶ 78. Feng teaches away from lower dhBBR doses. Additionally, Dr. Shebuski references data from the Caco-2 cell model to support his assertions, but the prior art calls into question the human translatability of the Caco-2 cell model. <i>See</i> Exh. 2175 at p. 1, 4-5 (describes differences in drug transporter expression between Caco-2 cells and small intestinal tissue) and Exh. 2176 at p. 14 ("Comparing human duodenum with Caco-2 cells, more than 1000 genes were
--	---

	determined to have at least a 5-fold difference in expression. A 2- to 595-fold difference was observed in expression of transporters, channels, and metabolizing enzymes between human duodenum and Caco-2 cells.”). This teaches away, or at least discourages, the direction Petitioner and Dr. Shebuski attempt to force the prior art to take, by showing that Caco-2 cells are not adequate correlates of human intestinal tissue, such that extrapolating dosages between Caco-2 cells and human beings, without more, is ill-advised. <i>See</i> Exh. 2108 at ¶ 80 (“It would be difficult for a POSITA to transfer cell culture data to humans with a reasonable likelihood of success because a cell culture does not replicate human physiology; rather, it consists of a homogeneous population of cells maintained under optimized conditions and does not account for relevant systemic factors in absorption such as the gut microbiome. In my opinion, clinical translation should not be based on cell culture work.”). Neither
--	---

	Petitioner, nor Dr. Shebuski, grappled with the issue of the non-translatability of Caco-2 cells to living humans (<i>see</i> Exh. 1003 at ¶¶ 79, 86, 90), but rather, just assume the data is transferable, which Exhs. 2175 and 2176 show that it is not that simple. <i>See also</i> Exh. 2183 at ¶ 227. In fact, Dr. Shebuski’s assertions in ¶ 90 of his declaration are hindsight-motivated as evidenced by his use of “[r]egardless.” It is not “regardless.” Dr. Shebuski is making an unsupported, unexplained, and in light of Exhs. 2175 and 2176, an unwarranted assumption. This is a significant oversight and deficiency in Petitioner’s Ground 3 obviousness position, because without it, the dhBBR concentrations are not close to being within the claimed range. Furthermore, Petitioner and Dr. Shebuski heavily rely on data from Figs. 3(b)-3(d) of Feng (<i>see e.g.</i> Paper 2 at 16, 46 and Exh. 1003 at ¶¶ 79, 86). That data is suspect, indicating it was, at best, a
--	---

	preliminary test experiment on three animals (n=3), with very large error bars on the data, and without statistical significance. <i>See</i> Exh. 2108 at ¶ 79. To the extent Petitioner relies upon Figs. 3(b)-3(d) of Feng, which they do in support of Ground 3, its reliance is misplaced. <i>See</i> Exh. 2183 at ¶ 230. For these reasons, the combination of Zhang and Feng fail to teach each and every limitation of claim 1 of the ‘961 Patent.
--	---

Claims 2, 5, and 7:

Claim 2	
The method of claim 1 wherein the administration of dihydroberberine reduces fasting glucose levels.	Again, Zhang did not administer dhBBR. <i>See</i> Exh. 1006, generally. Zhang does not use the word “dihydroberberine” at all. <i>Id.</i> Dr. DeFilippi questions whether Zhang credibly showed a reduction of fasting blood glucose. <i>See</i> Exh. 2183 at ¶ 232.

	Feng does not teach that dhBBR reduces fasting glucose levels in humans. <i>See</i> Exh. 1007, generally. Accordingly, Zhang and Feng combined do not meet the limitations of claim 2.
Claim 5	
The method of claim 1 wherein the dihydroberberine is orally administered as a capsule or tablet.	Zhang does not teach the oral administration of dhBBR in a capsule or tablet. <i>See</i> Exh. 1006, generally (no references to “dihydroberberine” at all); <i>see also</i> Exh. 2109 at ¶ 59. Feng does not teach the oral administration of dhBBR in a capsule or tablet, either. <i>See</i> Exh. 1007, generally (no references to “pill,” “tablet,” or “capsule.”). Accordingly, Zhang and Feng combined do not meet the limitations of claim 5.

Claim 7	
The method of claim 1 wherein the dihydroberberine is administered at least once daily.	Zhang did not administer dhBBR. <i>See</i> Exh. 1006, generally. Zhang does not use the word “dihydroberberine” at all. <i>Id.</i> Petitioner (<i>see</i> Paper 2 at 59-61) and Dr. Shebuski (<i>see</i> Exh. 1003 at ¶¶ 99-102 do not show dhBBR administered once per day by the combination of Zhang and Feng. As noted, Zhang did not use dhBBR at all, and the dhBBR experiments by Feng did not entail at least once per day administration of dhBBR to humans. Dr. Shebuski’s references to what may happen to berberine in gut tissue from something other than a living human in terms of conversion to dhBBR is irrelevant. Claim 1 and its dependents are about administering dhBBR, not berberine, and what may happen to berberine in the gut. To attempt to remedy this deficiency in its <i>prima facie</i> case, Petitioner has to resort to other references (e.g., Turner) to try to fill in the gaps.

	This appears to be nothing more than hindsight reasoning that still utterly fails to account for the very high equivalent dose of dhBBR used in Feng (1945.9 mg/day) and its teaching away from dosage range called for by the claim language, into which Petitioner and Dr. Shebuski strain to try to fit. Accordingly, Zhang and Feng combined do not meet the limitations of claim 7.
--	--

D. Ground 4: Claim 6 is Not Obvious in light of Zhang in View of Feng Further in View of Turner

The prior art references identified for the combination for Ground 4 have already been discussed above, and that discussion is incorporated herein by reference. What follows is the claim chart for Ground 4 – Claim 6.

Claim 6:

The method of claim 1 wherein the dihydroberberine is orally administered as	Turner teaches the addition of dhBBR onto animal chow (<i>see</i> Paper 2 at 63 and Exh. 1003 at ¶ 106 – “powder mixed with food”), not the creation of a “food product” or “beverage product” that inherently
--	---

at least one of a food product or beverage product.	contains the dhBBR. <i>See</i> Exh. 1004, p. 2 (under “Animals”). Dr. DeFilippi takes exception that this is what is taught by Zang in view of Feng further in view of Turner. <i>See</i> Exh. 2183 at ¶¶ 249-259. Accordingly, Zhang and Feng combined in further view of Turner do not meet the limitations of claim 6 of the ‘961 Patent.
---	---

The foregoing facts and authorities, including in the claim charts, demonstrate that Petitioner’s obviousness challenge is deficient on all Grounds, and that the validity of Patent Owner’s claims should be upheld.

VII. ADDITIONAL POINTS SUPPORTING THE ABSENCE OF A MOTIVATION TO COMBINE OR MODIFY THE PRIOR ART

In addition to the points detailed by Patent Owner in its discussion of the specific prior art references above, including in its claim charts, Patent Owner notes the following additional points showing the absence of a motivation to combine or modify the prior art.

Regarding Turner in combination with Shaw, Petitioner’s reliance on Dr. Shebuski (¶¶ 44-47) to show a motive to combine or reasonable expectation of

success does not help. First, Dr. Shebuski asserted that Turner “**opines** that dhBBR can be effective for human diabetes treatment” (Exh. 1003 (¶ 44)) (emphasis added). The word “speculates” is more appropriate than “opines.” See Exh. 2183 at ¶¶ 92, 127-138. There is no evidence that anyone else utilized dhBBR in humans for managing glucose tolerance prior to Patent Owner’s application for the ‘961 Patent.

In ¶¶ 45-46 of his declaration, Dr. Shebuski asserted that it would have been obvious for a POSITA to launch clinical studies of dhBBR in humans based on Turner’s results on commonly used animal models for diabetes. Yet, no one did for *many years*. Turner (Exh. 1004, p. 1) was submitted for publication in 2007 and published in 2008. For the ensuing eight (8) years until Patent Owner filed its provisional patent application in April 2016, no clinical trials to test the effect of dhBBR on managing glucose tolerance were undertaken by anyone to the best of Patent Owner’s knowledge. Patent Owner understands that Petitioner did not initiate a clinical trial for dhBBR until 2024, more than sixteen (16) years after Turner’s speculation. This strongly suggest hindsight reconstruction by Petitioner, as was rejected in *Leo Pharmaceutical Products, Ltd. v. Rea*, 726 F.3d 1346, 1355 (Fed. Cir. 2013) (“Turi was publicly available in the prior art for twenty-two years before the '013 patent was filed, yet there is no evidence that anyone sought to improve Turi with vitamin D.”).

Paragraph 47 of Dr. Shebuski’s declaration similarly does not help. Chen had

nothing to do with glucose metabolism or dhBBR. It is non-analogous art, as referenced above. The mere fact that Chen administered berberine to humans for irritable bowel syndrome does not support a motivation to combine, or a reasonable expectation of success. Again, it is nothing more than an improper hindsight reconstruction of claim 1 of the '961 Patent.

VIII. ADDITIONAL POINTS SUPPORTING THE ABSENCE OF A REASONABLE EXPECTATION OF SUCCESS

In addition to the points detailed by Patent Owner in its discussion of the specific prior art references above, including in its claim charts, Patent Owner notes the following additional points showing the absence of a reasonable expectation of success with respect to Petitioner's prior art combinations.

Petitioner failed to demonstrate a reasonable expectation of success for any of its combinations of prior art in Grounds 1-4. The reasonable expectation of success must be for a method of managing glucose tolerance in a human (*see* Paper 2 at pp. 4, 29-30) by administering ~25-800 mg of dhBBR. Exh. 1001, claim 1.

Patent Owner's expert Dr. Hartung rightly stated, "The alleged prior art relied upon by Petitioner for obviousness primarily provides short-term efficacy and pharmacokinetic observations in rodents and in vitro systems, and it therefore offers – at most – hypotheses rather than a reliable prediction of the claimed human glucose-tolerance outcomes and dose range." Exh. 2107 at ¶ 60.

A. Dr. Thomas Hartung Opines That There is no Reasonable Expectation of Success

Dr. Hartung has dedicated much of his professional life as a medical doctor and scientist to “the scientific question directly relevant to this proceeding: how reliably can preclinical evidence, especially animal studies, predict outcomes in humans?” *Id.* at ¶ 4. He has extensively written on the topic (*see e.g.* Exhs. 2028, 2032) and consulted on the topic (Exh. 2107 at ¶¶ 9, 11). With that background and experience, Dr. Hartung opined that “approximately 95% of drug candidates that enter clinical development ultimately fail, and that these failures are overwhelmingly linked to the inability of animal studies to predict human efficacy and safety,” (*Id.* at ¶ 5), that “humans and rats are very different” (*Id.* at ¶ 7), and that “available before 2016 (or in post-2016 literature that describes systems and the state of the prior art that existed as of April 2016) overwhelmingly demonstrated that no such expectation would have been reasonable (*Id.* at ¶ 8). Dr. DeFelippi concurs with Dr. Hartung. *See* Exh. 2183 at ¶¶ 41, 85-87.

Dr. Hartung further noted that a direct extrapolation of Turner’s results to humans “must contend with interspecies differences in metabolism and exposure rather than treating DHB as a ‘direct’ human active agent.” *See* Exh. 2107 at ¶ 62. Dr. Hartung cuts to the chase when he opines, “The patent discloses methods of administering dihydroberberine (DHB) to humans to achieve measurable improvements in glucose tolerance - outcomes that could not be predicted from

preclinical evidence due to known species differences in metabolism, mitochondrial function, and intestinal pharmacokinetics.” *Id.* at ¶ 34. He bases this opinion on the fact that, “[a]nimals, including rodents, differ from humans in fundamental features relevant to glucose metabolism, including mitochondrial regulation, glucoregulatory hormone dynamics, gut microbiota composition, intestinal enzyme expression, and hepatic metabolism.” *Id.* at ¶ 37. He added that, “[t]hese differences routinely produce misleading efficacy signals in rodent diabetes models that do not reproduce in humans.” *Id.*

Dr. Hartung supporting his knowledge and experience as to the lack of a reasonable expectation of success in translating preclinical lab results to humans by pointing to a study:

Begley and Ellis (2012) from Amgen in Nature “*Raise standards for preclinical cancer research ... Fifty-three papers were deemed ‘landmark’ studies ... scientific findings were confirmed in only 6 (11%) cases. Even knowing the limitations of preclinical research, this was a shocking result.*” See Exh. 2073 at p. 002. These studies showing the limited predictive value of single animal studies found a lot of attention in 2011/2012 and the following years.

Id. at ¶ 38 (italics in original); *see also Id.* at ¶¶ 36, 67.

Dr. Hartung further noted that,

My 2013 analysis of clinical trial attrition demonstrated that approximately 95% of drug candidates that enter clinical development ultimately fail, and that these failures are overwhelmingly linked to the inability of animal studies to predict human efficacy and safety.

Id. at ¶ 5 (citing Exh. 2028).

Simply put, 5-11% does not provide for a reasonable expectation of success. It provides for nearly a 90-95% expectation of failure.

Dr. Hartung's entire declaration (Exh. 2107) is a testament to the lack of translatability of preclinical research in lab animals, and thus, a lack of a reasonable expectation of success in humans. One of his key conclusions:

In my scientific judgment, the invention identifies a specific human directed administration strategy for DHB that overcomes the barriers known and that existed in 2016, and yields clinically relevant outcomes that were not reasonably predictable based on rodent studies or prior berberine research.

Id. at ¶ 35.

B. Dr. Chad M. Kerksick Opines That There is no Reasonable Expectation of Success

Patent Owner's scientific advisory board member, Dr. Kerksick (Exh. 2108 at ¶ 5), also provided statements and opinions addressing the lack of a reasonable expectation of success in Petitioner's petition. These are addressed in additional detail in Paper 8 at pp. 50-56 and incorporated herein by reference.

Briefly, Dr. Kerksick noted the substantial differences in the gut microbiota between rodents and humans as a key factor limiting any expectation of translatability of findings from rodents to humans, and thus, refuting a reasonable expectation of success. *See* Exh. 2108 at ¶¶ 32-40. Dr. Kerksick noted this issue as to Feng, in particular. *Id.* at ¶¶ 83, 84.

The same is true as to the differences between rodents and humans as to glucose metabolism itself. *Id.* at ¶¶ 41-44.

C. Dr. Qiang Tong Opines That There is no Reasonable Expectation of Success

Dr. Tong opined that even if there was a motivation to combine references to test dhBBR for managing glucose tolerance in humans, the prior art still did not provide a reasonable expectation of success. *See* Exh. 2109 at ¶ 36. Dr. Tong noted that the "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." *Id.* at ¶ 37. Dr. Tong then supported his opinion with

examples from the scientific literature. *Id.* at ¶¶ 37-41; Exhs. 1011, 2020, 2078, 2085. This supports the absence of a motivation to combine as well; or, at a minimum, dampens reasonable enthusiasm to combine, if any.

Regarding Turner, in particular, Dr. Tong continued by noting that, “Turner’s data suffers from multiple translational limitations, including exclusive use of young male rodents and the use of intraperitoneal injection of glucose into C57Bl/6J mice with a known mutation predisposing mice to glucoregulatory defect (Fergusson 2014, Exh. 2086).” *See* Exh. 2109 at ¶ 42.

Dr. Tong also identified issues with the non-physiological feeding paradigm used on inbred rats in Turner and its effects on other parameters that influence glucose metabolism such that a reasonable expectation of success in terms of translating the results from lab rats to living humans is speculative or questionable, not reasonable. *See* Exh. 2109 at ¶¶ 43-48, 53.

For at least the foregoing reasons, as well as those stated above in the discussion of the prior art references relied on by Petitioner, including in the claim charts, a POSITA would not have had a reasonable expectation of success as to the invention claimed in the Challenged Claims. Thus, Petitioner’s obviousness challenge fails on this basis as well.

IX. SECONDARY CONSIDERATIONS OF NONOBVIOUSNESS FURTHER DEMONSTRATE THE PATENTABILITY OF THE CHALLENGED CLAIMS

Secondary considerations of nonobviousness, each having a nexus to the claim language, further support the nonobviousness of the Challenged Claims.

A. Legal Standard

Objective evidence of nonobviousness – sometimes called “secondary considerations” or “objective indicia” – **must** be considered when present. *Apple, Inc. v. Samsung Electronics Co., Ltd.*, 839 F.3d 1034, 1048 (Fed. Cir. 2016). Objective indicia of nonobviousness include: (1) commercial success, (2) copying, (3) industry praise, (4) skepticism, (5) long-felt but unsolved need, and (6) failure of others. *Transocean Offshore Deepwater Drilling, Inc. v. Maersk Drilling U.S., Inc.*, 699 F.3d 1340, 1349-56 (Fed. Cir. 2012). This evidence serves as a safeguard against hindsight and against reading into the prior art the teachings of the invention at issue. *Graham v. John Deere Co.*, 383 U.S. 1, 36 (1966); *Apple v. Samsung*, 839 F.3d at 1052-58. Evidence of secondary considerations “may often be the most probative and cogent evidence in the record” and “may often establish that an invention appearing to have been obvious in light of the prior art was not.” *Stratoflex, Inc. v. Aeroquip Corp.*, 713 F.2d 1530, 1538–39 (Fed. Cir. 1983).

Secondary considerations evidence must have a “nexus” between the merits of the claimed invention and the objective evidence. *In re GPAC*, 57 F.3d 1573,

1580 (Fed. Cir. 1995). The existence of a nexus can be shown in two ways: (1) presumption of nexus or (2) showing that the evidence is a direct result of the unique characteristics of the claimed invention. *Volvo Penta of the Americas, LLC v. Brunswick Corp.*, 81 F.4th 1202, 1210 (Fed. Cir. 2023). A patent owner is entitled to a *presumption of nexus* when it shows that the asserted objective evidence is tied to a specific product that “embodies the claimed features and is coextensive with them.” *Brown & Williamson Tobacco Corp. v. Philip Morris, Inc.*, 229 F.3d 1120, 1130 (Fed. Cir. 2000). When a nexus is presumed, “the burden shifts to the party asserting obviousness to present evidence to rebut the presumed nexus.” *Id.*; *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1365 (Fed. Cir. 2023).

B. The Invention Claimed in the ‘961 Patent is a Commercial Success

Patent Owner demonstrates the substantial commercial success of the invention claimed in the Challenged Claims through the Declaration of Stephen A. Holzen. *See* Exh. 2181.

Mr. Holzen determined that commercial success exists for dhBBR supplements. *Id.* at ¶¶ 83-110. He based his conclusions on industry data, financial data from Patent Owner (e.g., sales, gross profits, pricing, customer count) (*Id.* at ¶¶ 83-93), as well as some financial data and deposition testimony from a customer of Petitioner (*Id.* at ¶¶ 94-99), and “Other External Demand Determinants” such as broader market conditions, advertising, and pricing metrics (*Id.* at ¶¶ 100-109).

Based on his analysis, Mr. Holzen concluded:

it is my opinion that the patented invention described in the ‘961 Patent is a commercial success. It is also my opinion that the commercial success of the patented invention derives from the benefits and advantages identified in the ‘961 Patent.

Id. at ¶ 110.

The aforementioned commercial success has a nexus with the Challenged Claims as it pertains to glucose management, glucose tolerance, and blood sugar control. *Id.* at ¶¶ 76-82, 107, 110 and Exhs. 2115, 2142. Mr. Holzen opines that “the comparatively broader scope of the ‘961 Patent claims ... capture the fundamental technology underlying the commercial product, rather than merely isolated improvements” and that “the broader claims of the ‘961 Patent are directed to core aspects of the technology that consumers and the marketplace value.” *See* Exh. 2181 at ¶¶ 81, 82. Mr. Holzen further opines that the commercial success of Patent Owner’s GlucoVantage product is consistent with and attributable what is covered by the ‘961 Patent. *Id.* at ¶ 82. He concludes by noting that:

the economic evidence tends to show a nexus between: (i) the claimed characteristics associated with the patented invention; (ii) the product attributes emphasized in supply-

side marketing materials; and (iii) the product characteristics valued by consumers. From an economic perspective, this consistency supports my conclusion that the patented characteristics are tied to consumer demand and commercial success.

Exh. 2181 at ¶ 107; *see also* ¶ 110 therein.

The foregoing, as well as the contents of Mr. Holzen's declaration (Exh. 2181), demonstrate that the sales and commercial success of both Patent Owner's and Petitioner's dhBBR products are directly tied claim 1 of the '961 Patent and its dependents, thus creating a presumption of nexus. *Brown & Williamson*, 229 F.3d at 1130.

C. The Invention Claimed in the '961 Patent Addressed a Long-Felt but Unsolved Need

A long-felt, but unsolved need to administer dhBBR to humans to manage glucose tolerance clearly existed before Patent Owner filed its application for the '961 Patent, as recognized by clinicians at the time and even Petitioner thereafter. "Evidence of a long-felt but unresolved need can weigh in favor of the non-obviousness of an invention because it is reasonable to infer the need would not have persisted had the solution been obvious." *See Apple, Inc.*, 839 F.3d at 1056.

The scientific literature reflects a broad unmet need for additional glycemic control beyond existing therapies. A 2015 article by Raccach et al. evaluated patients

with type 2 diabetes. *See* Exh. 2167. The study found that a substantial percentage of patients continued to experience residual hyperglycemia despite achieving fasting plasma glucose control. *Id.* at p. 1 (Abstract – under “Conclusions”). The authors concluded that these findings indicated a significant unmet need for additional methods of postprandial (post-food consumption) glycemic control. *Id.* at p. 1, 8.

Another scientific article from 2014 documented that, “Suboptimal blood glucose control among patients with type 2 diabetes continues to support the need for new pharmacologic approaches” (*see* Exh. 2172 at p. 1 (Abstract – under “Background”), and that, “Despite considerable advances in the therapy for type 2 diabetes, blood glucose control remains suboptimal.” *Id.* at 1 (under “Introduction”).

Additionally, literature describing berberine, a compound used “for centuries” to support metabolic balance, explains that its effectiveness “has always been capped by one major hurdle: poor absorption,” and that conversion into its active form is “often inefficient and incomplete.” These statements demonstrate that, despite longstanding recognition of berberine’s therapeutic potential, its utility remained limited by bioavailability constraints (*see* Exh. 2168 at p. 2).

Petitioner’s own paid content from 2025 recognized the drawbacks of berberine as a potential treatment for “glucose control” because of its “low bioavailability” and “poor intestinal absorption.” *See* Exh. 2165 at p. 1, 4. Petitioner then purported to be the innovator to “step forward to test the safety of Berberine

and Dihydroberberine” (*Id.* at p. 4), despite that Patent Owner has done that years before with its patent application and clinical trial. *See* Exh. 2173 at pp. 4-21 (p. 1-3 of exhibit filed with motion to seal).

Dihydroberberine-specific evidence further supports a presumption of nexus between the claimed invention, Patent Owner’s specific product, and this long-felt need. For example, the article titled “GlucoVantage®: Unlocking the True Potential of Dihydroberberine” explains that Berberine “has long been recognized for its potential to support healthy blood sugar metabolism,” but that it “faces major limitations due to poor absorption and a tendency to cause digestive discomfort.” *See* Exh. 2169 at p. 1. The article states that Petitioner’s GlucoVantage® “was created to help address these drawbacks,” and states that it is “[d]esigned for enhanced bioavailability and a gentler impact on digestion.” *Id.*

Accordingly, the record demonstrates a clear through-line: the field recognized a persistent unmet need for improved glucose control; existing berberine compounds were constrained by bioavailability limitations, and the invention embodied in Patent Owner’s GlucoVantage® product and set forth in claim 1 and its dependents in the ‘961 Patent addressed that need, as shown in the next section. A presumption of nexus applies. *Brown & Williamson* at 1130.

D. The Invention Claimed in the ‘961 Patent Received Industry Praise
Petitioner itself, a direct competitor of Patent Owner, praised Patent Owner’s

invention, which demonstrates non-obviousness. As the Federal Circuit has explained, “[e]vidence that the industry praised a claimed invention or a product that embodies the patent claims weighs against an assertion that the same claimed invention would have been obvious. Industry participants, especially competitors, are not likely to praise an obvious advance over the known art.” *Apple Inc.*, 839 F.3d at 1053.

In Exhibit 2173, which has been filed with a motion to seal given Petitioner’s counsel’s designation of the documents as highly confidential in the parallel litigation, in response to a question from a potential customer (*see* Exh. 2173 at p. 1), a representative of Petitioner touted the benefits of Petitioner’s dhBBR by pointing to a scientific article about the benefits of dhBBR wherein the study in the article was funded by *Patent Owner* and the dhBBR used in the study was supplied by Patent Owner (*Id.* at p. 8, 20). Petitioner’s representative expressly identified “lowering blood sugar” as a health function of dhBBR. This supports non-obviousness inasmuch as it establishes a presumption of nexus between the praise from a competitor and Patent Owner’s dhBBR *product* and invention claimed in the ‘961 Patent, including the limiting preamble and elements of claim 1. *Brown & Williamson* at 1130.

Additionally, Patent Owner’s patented method and corresponding product, GlucoVantage®, has been praised within the industry. For example, a 2025 recent

scientific review touts dhBBR, including Patent Owner's GlucoVantage® product and Petitioner's GlucoSober® product⁶, as a "true breakthrough" that "reduce[s] blood glucose levels," "reduces fasting blood glucose," and "enhance[s] ... glycemic control." *See* Exh. 2166 at pp. 4, 6, 7. Thus, the article directs praise to the limitations of claim 1 of the '961 Patent.

Furthermore, the industry noted and praised the glucose-related benefits of dhBBR based on the first human clinical trials conducted with dhBBR, particularly Patent Owner's dhBBR. *See* Exh. 2171 at pp. 1, 2, 4.

The foregoing examples demonstrate that the industry praised the appearance of dhBBR in the market, including Patent Owner's own product, and connected it to the limitations of claim 1 of the '961 Patent and its dependents. Again, a presumption of nexus applies. *Brown & Williamson* at 1130.

In summary, the commercial success, long-felt but unsolved need, and industry praise evidence, tied to Patent Owner's product and the patented method, demonstrate that the invention claimed in the Challenged Claims of the '961 Patent are not obvious.

⁶ Notably, Petitioner's GlucoSober® product is the subject of a U.S.-registered trademark (Reg. No. 7,932,736) in class 5, and includes in the identification of goods, "Dietary supplements for lowering glucose levels" and "Nutritional supplements for lowering glucose levels." *See* Exh. 2170. This is a further admission that Petitioner's GlucoSober dhBBR product has a nexus to the claims of the '961 Patent.

X. CONCLUSION

For the aforementioned reasons, Petitioner's petition fails to demonstrate that any of the Challenged Claims of the '961 Patent are obvious.

Date: July 7, 2026

Respectfully submitted,

/s/ Mark D. Nielsen
Mark D. Nielsen
Registration No. 52,068
SCHEEF & STONE, LLP
2600 Network Blvd., Suite 400
Frisco, Texas 75034
Telephone: 214-472-2100
Facsimile: 214-472-2150
mark.nielsen@solidcounsel.com

CERTIFICATE OF SERVICE

Pursuant to 37 C.F.R. § 42.105(b), the undersigned hereby certifies that a copy of this **PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.'S RESPONSE TO PETITION** has been served on July 7, 2026 upon the following litigation counsel via electronic means:

- John Handy, RIMON PC (john.handy@rimonlaw.com)
- Jason Xu, RIMON PC (jason.xu@rimonlaw.com)
- Hua Chen, SCIENBIZIP, PC (HuaChen@ScienBiziPPC.com)

Date: July 7, 2026

Respectfully submitted,

/s/ Mark D. Nielsen
Mark D. Nielsen
Registration No. 52,068
Counsel for Patent Owner

**CERTIFICATE OF COMPLIANCE WITH WORD COUNT
REQUIREMENTS UNDER 37 C.F.R. § 42.24**

Under 37 C.F.R. §§ 42.24(b)(2) and 42.24(d), the undersigned certifies that this **PATENT OWNER NANJING NUTRABUILDING BIO-TECH CO., LTD.’S RESPONSE TO PETITION** complies with the word count limitation in that it contains 13,636 words.

This paper also complies with the typeface requirements of 37 C.F.R. § 42.6(a)(2)(ii) and the type style requirements of 37 C.F.R. § 42.6(a)(2)(iii) and (iv).

Date: July 7, 2026

Respectfully submitted,

/s/ Mark D. Nielsen

Mark D. Nielsen

Registration No. 52,068

Counsel for Patent Owner