

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK,

Patent Owner.

Case No. IPR2024-00313
U.S. Patent No. RE47,045

PATENT OWNER RESPONSE

I.	Introduction.....	1
II.	Technology Background.....	4
III.	Level of Skill in the Art.....	6
A.	Level of Skill in the Art for Treating Lipofuscin-Associated Diseases	6
B.	Petitioner’s Declarants Are Not POSAs	10
1.	Dr. Calman Is a Generalist.....	10
2.	Dr. Guengerich Is an Enzymologist.....	12
IV.	Claim construction.....	12
V.	Nonobviousness.....	14
A.	Vitamin A Supplementation Was Contraindicated for Diseases Associated with Lipofuscin Accumulation	16
1.	Vitamin A Supplementation Was Taught Away From Because It Could Increase Harmful Lipofuscin Accumulation	17
2.	<i>Ortho</i> Attributes No Therapeutic Activity to Vitamin A	21
B.	A POSA Would Not Have Been Motivated to Administer C ₂₀ -D ₃ -Vitamin A To Slow <i>Mata</i> ’s Hypothetical Pathway.....	24
1.	Petitioner’s Abandoned “Likely” Rate-Limiting Argument	26
2.	The Petition Fails to Show the 1,5 Shift Was “Likely” Rate Limiting	29
3.	The Petition’s Ancillary Arguments Fail to Establish A Motivation.....	35
a.	<i>Mata</i> and <i>Fishkin</i> Do Not Suggest Targeting the 1,5 Shift Specifically	36

b.	General Deuterium Disclosures Provide No Specific Motivation	37
c.	<i>Roth</i> and <i>Itou</i> Provide Neither an Expectation of a Large KIE nor a Motivation to Target the 1,5 Shift.....	40
C.	No Reasonable Expectation of Success	44
1.	“Effective Amount” Not Reasonably Expected	44
2.	Petitioner’s Ancillary Arguments Fail.....	47
D.	Long-Felt Need, Failure of Others, and Unexpected Results Support the Non-Obviousness of the ’045 Patent.....	48
1.	Long-Felt But Unmet Need For The Treating Macular Degeneration That Others Tried But Failed To Satisfy.....	49
2.	Alkeus’s ALK-001 For the Treatment of AMD and Stargardt’s Disease Meets the Long-Felt Need	51
3.	Alkeus’s ALK-001 Overcame Skepticism and Was Widely Praised	53
4.	Unexpected Results of the Claimed Method	55
E.	Additional Deficiencies of Ground 1 (Ortho Pharma and Olson 1988): Claims 1-9, 19-23, 25-26, 28-36, 46-50, and 52-53	57
1.	No Motivation to Combine with a Reasonable Expectation of Success	57
2.	Retarding the Accumulation of a Lipofuscin Pigment (claims 1 and 2-9, 19-23, 25-26).....	58
3.	MD (claims 4, 28, 29-31, 46-50, 52-53) and AMD (5-9, 32-36)	59
4.	Forms A2E <i>in vitro</i> About 7 Times Slower (claim 9, 36, 53)	59
F.	Additional Deficiencies of Ground 2 (Ground 1 in Further View of <i>Mata</i>): Ground 1 + Claims 10-15, 18, 37-42, and 45	59

1.	No Motivation to Combine with a Reasonable Expectation of Success	60
2.	Dry (non-neovascular) AMD (claim 10, 37), Stargardt’s Disease (claim 11-15, 38-42), and MD + ABCA4 Gene Mutation (claim 18, 45)	61
3.	Forms A2E <i>in vitro</i> About 7 Times Slower (claim 15, 42)	61
G.	Additional Deficiencies of Ground 3 (Ground 1 and 2 in view of <i>Widder</i>): Claims 16-17, 24, 27, 43-44, 51, and 54	61
1.	No Motivation to Combine with a Reasonable Expectation of Success	62
2.	Vitelliform or Best Disease, Sorsby’s Fundus Dystrophy, Retinitis Pigmentosa, and Malattia Leventinese (claim 16 (+17), 43 (+44)).....	62
3.	Phosphatidylglycerol (Claims 24, 51)	62
4.	Directly to the Eye (Claims 27, 54)	63
VI.	Petitioner Concealed its Real Parties In Interest	63

TABLE OF AUTHORITIES

	Page(s)
Federal Cases	
<i>Abbott Laboratories v. Sandoz, Inc.</i> , 544 F.3d 1341 (Fed. Cir. 2008)	45
<i>Adaptics Ltd. v. Perfect Co.</i> , Case IPR2018-01596, Paper 20 (PTAB March 6, 2019)	44
<i>Apple Inc. v. Samsung Electronics Co., Ltd.</i> , 839 F.3d 1034 (Fed. Cir. 2016) (<i>en banc</i>)	49
<i>Arctic Cat Inc. v. Polaris Industries, Inc.</i> , 795 Fed. Appx. 827 (Fed. Cir. 2019)	28, 58
<i>Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc.</i> , IPR2022-00579, Paper 72 (PTAB Aug. 29, 2023)	9
<i>Daiichi Sankyo Co. v. Apotex, Inc.</i> , 501 F.3d 1254 (Fed. Cir. 2007)	7
<i>In re Dow Chemical Co.</i> , 837 F.2d 469 (Fed. Cir. 1988)	53
<i>Duke Univ. v. BioMarin Pharm. Inc.</i> , 685 F. App'x 967 (Fed. Cir. 2017)	28, 30, 37, 38
<i>Eli Lilly & Co. v. Teva Pharms. Int'l GmbH</i> , 8 F.4th 1331 (Fed. Cir. 2021)	12, 13, 44, 46
<i>Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.</i> , 276 F. Supp. 3d 629 (E.D. Tex. 2017), <i>aff'd</i> , 739 F. App'x 643 (Fed. Cir. 2018)	29, 36, 38
<i>Genetics Inst., LLC v. Novartis Vaccines and Diagnostics, Inc.</i> , 655 F.3d 1291 (Fed. Cir. 2011)	37
<i>In re Gordon</i> , 733 F.2d 900 (Fed. Cir. 1984)	21

<i>In re Gurley</i> , 27 F.3d 551 (Fed. Cir. 1994)	16, 17
<i>Harmonic Inc. v. Avid Tech., Inc.</i> , 815 F.3d 1356 (Fed. Cir. 2016)	44
<i>Impax Lab 'ys., Inc. v. Lannett Holdings Inc.</i> , 246 F. Supp. 3d 1024 (D. Del. 2017), <i>aff'd sub nom.</i> 893 F.3d 1372 (Fed. Cir. 2018).....	8
<i>Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino</i> , 738 F.3d 1337 (Fed. Cir. 2013)	53
<i>Jansen v. Rexall Sundown, Inc.</i> , 342 F.3d 1329 (Fed. Cir. 2003)	13
<i>Knauf Insulation, Inc. v. Rockwool Intl. A/S</i> , 788 Fed. Appx. 728 (Fed. Cir. 2019).....	57
<i>KSR Int'l Co. v. Teleflex Inc.</i> , 550 U.S. 398 (2007).....	23, 24
<i>Kyocera Senco Indus. Tools Inc. v. ITC</i> , 22 F.4th 1369 (Fed. Cir. 2022)	10
<i>Leo Pharm. Prods., Ltd. v. Rea</i> , 726 F.3d 1346 (Fed. Cir. 2013)	50
<i>Intel Corp. v. Koninklijke Philips N.V.</i> , No. 2022-2034, 2024 WL 725243 (Fed. Cir. Feb. 22, 2024).....	60
<i>Medit Corporation v. 3Shape A/S</i> , IPR2023-01316, Paper 6 (PTAB Mar. 29, 2024)	35
<i>Metalcraft of Mayville, Inc. v. The Toro Co.</i> , 848 F.3d 1358 (Fed. Cir. 2017)	21
<i>Mintz v. Dietz & Watson, Inc.</i> , 679 F.3d 1372 (Fed. Cir. 2012)	8
<i>Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH</i> , 139 F.3d 877 (Fed. Cir. 1998)	8

<i>Neptune Generics LLC v. Auspex Pharms., Inc.</i> , IPR2015-01313, Paper 25 (PTAB Dec. 9, 2015)	29
<i>Orexo AB v. Actavis Elizabeth LLC</i> , 903 F.3d 1265 (Fed. Cir. 2018)	34, 50
<i>Pfizer, Inc. v. Apotex, Inc.</i> , 480 F.3d 1348 (Fed. Cir. 2007)	35, 36
<i>Power Integrations, Inc. v. Fairchild Semiconductor Int'l, Inc.</i> , 711 F.3d 1348 (Fed. Cir. 2013)	48
<i>Rapoport v. Dement</i> , 254 F.3d 1053 (Fed. Cir. 2001)	13, 14
<i>In re Soni</i> , 54 F.3d 746 (Fed. Cir. 1995)	55
<i>Star Sci., Inc. v. R.J. Reynolds Tobacco Co.</i> , 655 F.3d 1364 (Fed. Cir. 2011)	37
<i>In re Stepan Co.</i> , 868 F.3d 1342 (Fed. Cir. 2017)	27
<i>Supernus Pharms., Inc. v. Actavis Inc.</i> , No. CV 14-07272, 2016 WL 901837 (D.N.J. Mar. 9, 2016)	9
<i>Teleflex, Inc. v. Ficosa North America Corp.</i> , 299 F.3d 1313 (Fed. Cir. 2002)	60, 62
<i>Tokio Marine & Fire Ins. Co. v. Grove Mfg. Co.</i> , 958 F.2d 1169 (1st Cir. 1992).....	11
<i>U. of Strathclyde v. Clear-Vu Lighting LLC</i> , 17 F.4th 155 (Fed. Cir. 2021)	47
<i>Unigene Labs., Inc. v. Apotex Inc.</i> , 655 F.3d 1352	47, 60
<i>In re Wright</i> , 569 F.2d 1124 (CCPA 1977).....	50

Federal Statutes

35 U.S.C. § 312(a)(2).....64

35 U.S.C. § 312(a)(3).....44, 58

I. INTRODUCTION

Alkeus Pharmaceuticals (Patent Owner's real party-in-interest) is developing deuterated vitamin A (ALK-001) for the treatment of macular degeneration ("MD"), as claimed in the challenged patent¹. Its mechanism of action entails retarding the accumulation of toxic lipofuscin pigments (such as "A2E") that cause blindness by irreversibly damaging the retina. Clinical results have now demonstrated efficacy of ALK-001 in treating both Stargardt's disease, a MD that leads to profound blindness in children, and geographic atrophy ("GA"), an advanced form of age-related macular degeneration ("AMD") which is the number one cause of blindness in the United States, affecting millions. These results evidence that the claimed method overcomes a long-felt need, widespread failures, and concern that administering deuterated vitamin A would increase rather than decrease lipofuscin.

The Petition fails to establish the obviousness of administering vitamin A—the substrate for the visual cycle that also generates the "ATR" precursor to lipofuscin. To the contrary, vitamin A *deficiency* prevented lipofuscin accumulation and, as Petitioner's ophthalmologist (Dr. Calman) testified, *increased* vitamin A could *increase* toxic lipofuscin formation. EX2104, 14:16-22,

¹ Patent No. RE47,045 ("the '045 patent").

15:8-17; EX2192 ¶¶216-222. For this reason, the art taught away from vitamin A supplementation, especially for Stargardt's disease. EX2192 ¶¶63-69. The Petition does not show how its proposed combination of a mixture of nutritional supplements (*Ortho*, EX1008) and C₂₀-deuterated retinoids for non-therapeutic use (*Olson* 1988, EX1006) would overcome this contraindication. Adding *more* vitamin A is not “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway.” EX1010 (“*Mata*”), 6.

Instead, the Petition's speculative “kinetic isotope effect” (KIE) argument is also dead on arrival. On cross examination, its chemistry declarant (Dr. Guengerich) abandoned the key premise that a “1,5 shift” in *Mata*'s hypothetical A2E biosynthetic pathway was “likely” rate limiting, admitting he could not say this, that a POSA would not be looking for the rate-limiting step, and that other steps could be slower and rate-limiting. EX2103, 50:8-54:14, 76:10-77:24, 81:1-82:23; *see* EX1002 ¶¶98, 178, 181, 184, 260, 353). This about-face is unsurprising. A POSA had no reason to select the 1,5 shift out of the still speculative A2E pathway or expect it to be likely rate limiting. Dr. Guengerich's abandonment of his meritless “likely” rate-limiting-step argument strips the Petition of its alleged motivation to use deuterated vitamin A.

One clear and undisputed point from the Petitioner's art is that there were no viable treatments to reduce lipofuscin accumulation that causes MD. The need was

particularly significant for both Stargardt's disease, where any rate of slowing would be beneficial, and dry-AMD, which affects millions. Petitioner's exhibits document extensive research focused on *impeding* the visual cycle to reduce lipofuscin's necessary ATR precursor. This singular approach, however, had the direct and unavoidable effect of worsening night blindness and/or dark adaptation.

The invention of Dr. Ilyas Washington claimed here solved the long-felt need for retarding the accumulation of lipofuscin and treating MD without worsening night blindness and dark adaptation. Notably, prior to these proceedings and even prior to Alkeus's clinical results, Dr. Guengerich recognized the significance of Dr. Washington's invention. In 2010, before being retained by Petitioner, Dr. Guengerich was an editor at the *Journal of Biochemistry*, where he reviewed two of Dr. Washington's publications related to the invention and preclinical results. Dr. Guengerich and his reviewers described the first as:

an innovative paper on the use of deuterium in vitamin A to provide a significant kinetic isotope effect to slow down the rate of dimerization of retinaldehyde that leads to the production of ATR dimer, which is associated with the onset of macular degeneration.

EX2056, 2. They called the other's use of deuterated vitamin A "*quite novel*."²

EX2057, 1-2. These impartial prelitigation admissions are consistent with the additional praise the invention received based on clinical trial results of ALK-001 in Stargardt's disease and GA.

The '045 patent covers a groundbreaking therapy for rare disease with no existing treatment. Petitioner proposes an obviousness combination the art taught away from and relies on hindsight speculation contradicted by its declarant's admissions. Petitioner has not—and cannot—meet its burden to prove the challenged claims unpatentable.

II. TECHNOLOGY BACKGROUND

As of 2007, vitamin A had been studied for treating eye disorders for over a thousand years. EX1028, 1. The phenomena of kinetic isotope effect ("KIE") had been known for over half a century. *E.g.*, EX1047, 2. Deuterium (and tritium)-labeled retinoids—including C₂₀-D₃-vitamin A—had been synthesized and used to study vitamin A utilization for more than 20 years. EX1006 (metabolic studies); EX1007 (same); EX1019 (tracer); EX1045 (estimate body stores of vitamin A); EX1053 (assess total-body stores of vitamin A); EX1052 (to discover retinoid receptor ligands).

² ***Bolded italics*** denotes emphasis added unless otherwise noted.

The visual cycle involves a series of reactions that convert vitamin A between several of its forms, such as retinol and retinal, to enable vision. EX1033, 1-2. The visual cycle intermediate all-*trans*-retinal (ATR) can also form toxic lipofuscin pigments such as A2E and ATR-dimer that accumulate in the retina. *Id.* Macular degeneration was thought to be caused by toxic effects of these accumulated pigments. *E.g.*, EX1001, 1:65-2:8; EX1033, 1 (“Circumstantial evidence... has implicated retinal pigment epithelial (RPE) lipofuscin in the etiology of [AMD]....”). Lipofuscin accumulation was understood to be accelerated in Stargardt’s disease, where its early onset affects “children age 6 to 12 years causing rapid severe decline in visual acuity over 12 to 24 months.” EX2015, 2. Vitamin A is thus both a critical substrate for the visual cycle but also the source of toxic lipofuscin pigments.

One proposed strategy for treating MD was to reduce the formation of the toxic lipofuscin pigments by inhibiting the visual cycle. EX1001, 2:8-3:37. At the time, the art focused on inhibiting the visual cycle by reducing the levels of retinol (vitamin A) in the blood or by pharmacologically inhibiting visual cycle enzymes to lower ATR production and, in turn, decrease lipofuscin pigments. *E.g.*, EX2003, 9, 15-16; EX2064, 2; EX2052 ¶¶112-128. For example, the small molecule fenretinide was tested to lower the amount of retinol that entered the visual cycle from the bloodstream, limiting ATR and lipofuscin by limiting vitamin A.

EX1001, 3:23-31; EX1035, 1. Isotretinoin and TDH were tested to inhibit the enzyme RPE65, slowing the production of the ATR. EX1001, 2:57-3:22; EX2066, 1-2.

These strategies, however, were plagued by side effects that prevented their therapeutic use. *E.g.*, EX1001, 3:38-4:41. Since a functioning visual cycle is essential for vision and eye health, inhibiting the cycle led to “delayed dark adaptation and, poor vision in dim light or at night” that were “expected to make night vision worse in patients who already suffer from poor night vision.” *Id.*, 3:38-4:41; *see also* EX1031, 171, 222-224, 227; EX2090, 23.

It is this problem—reducing lipofuscin pigment formation *without* inhibiting the visual cycle—that the claimed invention solves. The inventor found that—contrary to the prior art—C₂₀D₃-vitamin A could reduce lipofuscin pigment formation and even lipofuscin deposits in animals *without* slowing the visual cycle. EX1001, 20:60-21:22, Fig. 7. Beyond these pre-clinical proofs, C₂₀ deuterated vitamin A has been clinically shown to treat macular degeneration, in particular in its aggressive Stargardt’s and advanced GA forms.

III. LEVEL OF SKILL IN THE ART

A. Level of Skill in the Art for Treating Lipofuscin-Associated Diseases

The POSA here would have had specialized knowledge in the biosynthesis and structure of lipofuscin pigments or related natural products from the broader

class of terpenoids (e.g., retinoids and bis-retinoids such as lipofuscin pigments, carotenoids, steroids) and/or methods to slow lipofuscin formation or accumulation to treat or ameliorate an ophthalmologic disorder, such as AMD or Stargardt's disease. *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256-57 (Fed. Cir. 2007) (holding district court erred in finding POSA was a general practitioner and finding level of skill in the art was a specialist in the relevant medical field). This is reflected in the complexity of the subject matter—"methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as macular degeneration, without or with reduced adverse visual effects," and the related unmet need and failures of other. Paper 2 ("Pet."), 7; EX1001; EX1010; §V.D. Those practicing in the art also had years of experience beyond a general practitioner.

More specifically:

The POSA would have an advanced degree (e.g., M.D., Ph.D., M.S., or equivalent), in a field related to medicine (with training in ophthalmology), and/or in chemistry, biochemistry, pharmaceutical science, or a related field with at least three years of experience researching biosynthesis and structure of naturally-occurring terpenoids (e.g., retinoids and bis-retinoids such as lipofuscin pigments, carotenoids, steroids) and/or methods to slow lipofuscin formation or accumulation to treat an ophthalmologic disorder, such as AMD or Stargardt's disease. The POSA may consult with others,

such as a biochemist or formulation scientist, to understand or explain the contents of the prior art.

EX2052 ¶¶25-34 (describing level of skill); EX2192 ¶¶23-30 (describing level of skill).³

Petitioner’s proposed definition is three-fold wrong.

First, it requires *no* specialized skill beyond a general ophthalmologist.

Second, it defines the POSA as one who, among other things, “had practical knowledge about... the deuterium isotope effect” (Pet., 7) and improperly “used the invention to define the problem that the invention solves.” *Mintz v. Dietz & Watson, Inc.*, 679 F.3d 1372, 1377 (Fed. Cir. 2012). Petitioner “[d]efining the problem”—specifically the POSA—“in terms of its solution reveals improper hindsight in the selection of the prior art relevant to obviousness.” *Monarch Knitting Mach. Corp. v. Sulzer Morat GmbH*, 139 F.3d 877, 881 (Fed. Cir. 1998). “As the adage goes, to a hammer everything is a nail.” *Impax Lab’ys, Inc. v. Lannett Holdings Inc.*, 246 F. Supp. 3d 1024, 1044 (D. Del. 2017), *aff’d sub nom.* 893 F.3d 1372 (Fed. Cir. 2018).

³ Patent Owner’s definition does not include “treatment” of lipofuscin-associated retinal diseases since no treatments were then available. Pet., 7.

Third, Petitioner improperly relies on a “team” proposal to combine separate opinions as to what would have been obvious from “the perspective of a chemist” and what would have been obvious from the “perspective of a clinician.”

EX1002 ¶¶98, 184; EX1004 ¶¶49, 53; *Celltrion, Inc. v. Chugai Seiyaku Kabushiki Kaisha, Genentech, Inc.*, IPR2022-00579, Paper 72 at 9 (PTAB Aug. 29, 2023)

(“We find no support in [*Daiichi*] *Sankyo* for Patent Owner’s contention that ‘a person of ordinary skill in the art can have the knowledge and experience of multiple individuals working across different arts.’”). While a POSA may have access to individuals skilled in other areas (e.g., a biochemist or formulation scientist) the same as they have access to the prior art as a whole, that is different from Petitioner’s aggregated POSA “team” combining *separate* allegations of obviousness from different perspectives. *See Supernus Pharms., Inc. v. Actavis Inc.*, No. CV 14-07272, 2016 WL 901837, at *2 (D.N.J. Mar. 9, 2016)

(“Defendants’ position that a POSA is ‘one or more of, or a team’... runs counter to the generally accepted definition of a POSA.”); EX1002 ¶98 (Dr. Guengerich addressing what “a person of ordinary skill in the art with the *perspective of a chemist* would have recognized....”); EX1004 ¶49 (Dr. Calman opining from the “perspective of a person of ordinary skill in the art *from the perspective of a clinician* who diagnoses and treats ophthalmologic disorders”).

B. Petitioner’s Declarants Are Not POSAs

“To offer expert testimony from the perspective of a skilled artisan in a patent case... a witness must at least have ordinary skill in the art. Without that skill, the witness’ opinions are neither relevant nor reliable.” *Kyocera Senco Indus. Tools Inc. v. ITC*, 22 F.4th 1369, 1376-78 (Fed. Cir. 2022). Petitioner’s declarants fail to meet this minimum standard.

1. Dr. Calman Is a Generalist

Dr. Calman lacks the minimum experience to qualify as a POSA or provide expert testimony in this proceeding.

Rather than being a POSA or substantive expert in the relevant art, he is a general practice ophthalmologist and a professional witness. He actively advertises himself as a witness for hire, with “General Specialties” of “Ophthalmology and Optometry” and “Keyword/Search Terms” unrelated to the specific subject matter of the ’045 patent.

Specialties & Experience of this Expert Witness

General Specialties: Ophthalmology and Optometry

Keywords/Search Terms: Cataract, Glaucoma, Diabetic Retinopathy, eye, vision, eye injury, eye injuries, retina, macula, eye surgery, vision loss, patent, antitrust, eyedrops, pharmaceuticals, coding, reimbursement

EX2017, 1; *cf.* Pet., 7.

His career as an expert—having been deposed or testified approximately 79 times—dwarfs his contributions of 21 publications (many only addressing policy)

over 40 years. EX2104, 144:15-146:5 (6 of 21 publications are non-peer reviewed policy papers), 152:25-153:14; EX1005, 9-10. Indeed, three-quarters of Dr. Calman's income comes from witnessing. EX2104, 154:16-155:8; *Tokio Marine & Fire Ins. Co. v. Grove Mfg. Co.*, 958 F.2d 1169, 1174 (1st Cir. 1992) (holding that the district court "judge concluded, supportably, that [the expert] was 'more a professional witness than an expert in crane defects'" (citation omitted)).

Dr. Calman lacks experience researching biosynthesis and structure of naturally-occurring terpenoids (e.g., retinoids and bis-retinoids such as lipofuscin pigments, carotenoids, steroids) and/or methods to slow lipofuscin formation or accumulation to treat an ophthalmologic disorder, such as AMD or Stargardt's disease. *See* EX2104, 10:20-11:13. He does not attempt to treat Stargardt's patients, instead referring them to an expert. *Id.*, 11:15-13:14, 21:8-21, 48:24-50:25. And his clinical research experience is limited to diabetes, glaucoma, and monitoring ocular side effects. *Id.*, 146:6-25; EX1005, 11-12.

Unsurprisingly, lacking a relevant background, it is clear that Dr. Calman does not understand the art on which he relies and is forced to "defer to Dr. Guengerich." EX2104, 60:4-62:3, 62:4-63:8, 70:23-71:6, 76:7-78:1, 99:15:100:4. Dr. Calman further undermines his own credibility with evasive and nonresponsive testimony. *Id.*, e.g., 29:9-23, 35:3-36:2, 39:12-17.

2. Dr. Guengerich Is an Enzymologist

Dr. Guengerich also lacks the minimum experience to qualify as a POSA or provide expert testimony in this proceeding. His work focuses nearly exclusively on enzymatic reactions. EX2103, 127:3-10 (“I think essentially everything I’ve done is actually with enzymes, so it’s -- some may or may not apply.”). He lacks experience with lipofuscin formation.

He also lacks credibility. As detailed below, Dr. Guengerich abandoned his core opinion that the 1,5 shift was likely rate limiting in the formation of A2E.

§V.B.1. His contention that the C-H bond breaking was recognized in the art as slow is contradicted by his 2005 statement that the literature “had a tendency” to regard “C-H bond breaking as generally being relatively rapid.” EX2083, 1. In 2011, he did not disagree with his reviewers praised two of the inventor’s “novel” and “clinically important” papers; today, he argues the invention these papers described was obvious. EX2056, 1-2; EX2057, 2.

IV. CLAIM CONSTRUCTION

The preambles of independent claims 1 (“A method of retarding the accumulation of a lipofuscin pigment in a retina....”), 28 (“A method of treating a macular degeneration....”), and 29 (same) should all be construed as limiting as they “giv[e] life and meaning to the method step of each claim....” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1343 (Fed. Cir. 2021); *see*

EX2193 ¶46. This is consistent with the Board’s reasoning finding the claim 28 preamble limiting:

First, the Federal Circuit “has not hesitated to hold preambles limiting when they state an intended purpose for methods of using a compound.” *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1342 (Fed. Cir. 2021). And where, as here, the claims are directed to methods of using a compound for a specific purpose (i.e., treating a macular degeneration), and the method comprises a single step of administering that compound in an effective amount, the Federal Circuit “[has] generally construed statements of intended purpose in such method claims as limiting.” *Id.* at 1340.

* * *

The preamble of “treating a macular degeneration” is necessary to understand the patients to whom the substituted C₂₀-D₁-3-retinoid should be administered; thus, it limits the claim. *See Eli Lilly & Co.*, 8 F.4th at 1341–42 (citing *Jansen v. Rexall Sundown, Inc.*, 342 F.3d 1329, 1332–33 (Fed. Cir. 2003)); *Rapoport v. Dement*, 254 F.3d 1053, 1059 (Fed. Cir. 2001)....”).

Paper 13, Institution Decision (“ID”), 30-31.

The Board’s analysis applies equally to claims 1 and 29, where the preambles similarly (1) define the object of the “effective amount” as recited in the body of the claim and (2) provide antecedent for a “patient in need thereof,” as recited in the claim bodies. EX1001, claims 1, 29. Claim 29’s “macular

degeneration” preamble further provides antecedent for narrower macular degeneration conditions, e.g., claim 32 (“wherein the macular degeneration is age-related macular degeneration”), claim 38 (“wherein the macular degeneration is Stargardt disease”). *Id.*, claims 29, 32, 38.

Of the three independent claims, Petitioner has only argued that the claim 28 preamble is nonlimiting. *See* Pet., 23-24 (claim 28), 27 (claim 29), 29-30 (claim 1). As above, this position was and should be rejected. For claims 1 and 29, by contrast, Petitioner has treated both preambles as limiting. *E.g., id.*, 28 (alleging prior art to teach treating macular degeneration), 30 (alleging prior art to render obvious to “retard[ing] accumulation of A2E/lipofuscin”).

V. NONOBVIOUSNESS

All of Petitioner’s grounds share common defects that prevent it from establishing the obviousness of any claim.

First, the art taught vitamin A *deficiency* reduced lipofuscin accumulation and thus taught away from administering vitamin A for macular degeneration. Neither *Ortho*’s mixed nutritional supplements with vitamin A nor AREDS criticized use of beta-carotene as an antioxidant overcome the contraindication of supplementing vitamin A for reducing lipofuscin accumulation or treating macular degeneration.

Second, there was no reasonable basis to expect administering C20 deuterated vitamin A would slow the formation of A2E. Petitioner's argument that the 1,5 shift was "likely" a rate-limiting is unsupported by the art and was abandoned by Dr. Guengerich. Without this core assumption, Petitioner has failed to show why a POSA would have targeted the 1,5 shift specifically and thus fails to provide a motivation to combine *Olsen's* deuterated vitamin A with *Ortho*.

Third, none of the Petition's assertions provide a reasonable expectation of success of administering an effective amount of deuterated vitamin A to retard lipofuscin accumulation (claim 1 and dependents) or treat macular degeneration (claims 28-29 and dependents). To the contrary, a POSA would have expected supplemental vitamin A (deuterated or not) could only increase visual cycle byproducts, increase lipofuscin, and be harmful for macular degeneration.

Fourth, significant secondary indicia support the nonobviousness of the claimed invention. Despite significant efforts, macular degeneration linked to toxic lipofuscin accumulation, such as dry AMD and Stargardt's disease, remained untreatable. These secondary indicia include praise from Petitioner's chemist (Dr. Guengerich) and demonstrated clinical efficacy despite initial skepticism that deuterated vitamin A would exacerbate the condition.

In addition to these common flaws, each ground contains claim-specific defects that further prevent Petitioner from establishing the obviousness of any claim.

A. Vitamin A Supplementation Was Contraindicated for Diseases Associated with Lipofuscin Accumulation

The Petition asserts that *Ortho* motivated administering vitamin A to treat macular degeneration. Pet., 28. This contradicts the art, where vitamin A had long ago been tested and found unhelpful and taught away from vitamin A supplementation for diseases associated with lipofuscin accumulation due to its potentially detrimental effects. *In re Gurley*, 27 F.3d 551, 553 (Fed. Cir. 1994); *see also* EX2192 ¶¶64-69, 109-127, 210-222; EX2151, 4.

Vitamin A *deficiency* was seen as beneficial because underfeeding the visual cycle reduced ATR, a precursor to lipofuscin. EX1009, 47; EX2156, 3 (table II); EX1030, 1, 8; EX2104, 14:9-16:2; EX2192 ¶¶64-71. As Dr. Guengerich volunteered, adding additional vitamin A (per *Ortho*) is “counter[.]” and “diametrically opposed” to this strategy of reducing ATR formation. EX2103, 173:8-19, 176:16-177:10. Hence, vitamin A supplementation was contraindicated and discouraged, especially for rapidly progressing Stargardt’s disease. EX2164, 12; EX2133, 2; EX2110, 5; EX2158, 8; EX2104, 13:3-14, 20:17-21:2; EX2192 ¶¶103-105, 112-127, 216-222.

Where the art did teach vitamin A supplementation, it was limited to treating conditions associated with vitamin A deficiency. EX2192 ¶¶128-134. *Ortho*, for example, disclosed no function for vitamin A in its multi-component cocktail beyond preventing deficiency. EX1008, [0003], [0011]; EX2192 ¶¶149-152, 175-179. Such disclosures do not support the use of vitamin A to retard lipofuscin accumulation or treat MD.

1. Vitamin A Supplementation Was Taught Away From Because It Could Increase Harmful Lipofuscin Accumulation

“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 Gurley*, 27 F.3d at 553. Here, as confirmed by Petitioner’s declarants, *Mata*, *Widder*, and other art would have led a POSA “in a direction divergent from the path that was taken by the applicant”—specifically to *lower* vitamin A levels—and away from vitamin A supplementation that could increase harmful lipofuscin accumulation.

Macular degeneration was understood to result from damage to the retina caused by accumulation of toxic lipofuscin pigments, such as “A2E,” generated from starting material “ATR.” 2136, 1, 6; EX2003, 13; EX2052 ¶¶67-70; EX2192 ¶85. Since ATR is produced from vitamin A as part of the visual cycle, it

was understood that vitamin A deficiency—essentially underfeeding the visual cycle—would retard lipofuscin formation by reducing the ATR starting material. EX2104, 14:1-22; EX2156, 3 (Table II) (“Factors retarding lipofuscin formation.... Vitamin A deficiency); EX2110, 5 (“[B]y *reducing the level of the vitamin A cycle* and its intermediary products, *lipofuscin levels may be lowered*, with beneficial consequences for Stargardt, RP, CRD, and some AMD patients.”); EX2003, 1 (“Dystrophies resulting from the accumulation of toxic pigments can be treated pharmacologically by inhibiting the visual cycle, or limiting the supply of vitamin A to the eyes.”); EX2192 ¶¶64-69.

Applying this principle, all pharmacological strategies as of 2007 entailed inhibiting visual cycle enzymes to reduce excess ATR and thus A2E. EX2003, 14 (“Several approaches have been tested or proposed to slow accumulation of A2E. *All . . . ultimately limit the formation of all-trans-RAL....*”); EX2103, 199:18-203:7. For complementary reasons, vitamin A supplementation was discouraged as harmful where lipofuscin accumulation was a concern. EX2192 ¶¶216-221; EX2164, 12 (“Stargardt patients should avoid a diet high in vitamin A”); EX2110, 5; EX2133, 2 (“Because ABCA4 gene mutations seem to impair the processing of vitamin A, it has been suggested that vitamin A supplements may actually exacerbate Stargardt disease. Therefore, such vitamin supplements are not

recommended.”); EX2158, 8 (“Vitamin A should not be given to RP patients with mutations in *ABCA4*.”).

Dr. Calman confirmed this, testifying in detail that the literature—including *Mata* (EX1010)—would have directed against vitamin A supplementation for Stargardt’s patients:

- “And I recommend that [Stargardt’s patients] not consume excessive vitamin A.” (EX2104, 13:3-11);
- “[B]asically, the more substrate you’re inputting into the visual cycle, potentially that’s exacerbating the buildup of ATR, which is the lipofuscin precursor.” (*id.*, 14:9-22),
- “[M]ost clinicians, as far as I know today, do not recommend vitamin A supplementation for Stargardt’s” (*id.*, 15:8-18:15),
- *Mata* “is certainly one of the bases for” recommending against vitamin A supplementation for Stargardt’s patients. (*id.*, 18:16-20:9);
- “[T]hose who were aware of some of this experimental literature might have thought that restriction of vitamin A could be helpful in these patients.” (*id.*, 20:17-21:7); and
- Agreeing that “in terms of Stargardt’s patients that [he was] avoiding vitamin A supplementation to avoid creating more intermediate that can form into A2E and, specifically, ATR.” (*id.*, 22:11-17).

Dr. Guengerich similarly testified that vitamin A supplement (as in *Ortho*) is “*diametrically opposed*” to having “less material to go on and form these lipofuscin products.” EX2103, 172:23-177:20 (“[T]hose were actually almost countering each other in terms of giving vitamin A and also lowering retinal levels....”). He explained that *Ortho* teaching “giving more vitamin A” is the opposite of “hav[ing] less [starting] material to go on and form these lipofuscin products.” *Id.* And he agreed that “[d]ecreasing serum retinol levels for Widder is the opposite of *Ortho* increasing serum retinol levels.” *Id.*

The Petition misunderstands the pathophysiology of macular degeneration and ignores the art teaching away from vitamin A supplementation, paradoxically suggesting it would have been obvious to administer *more* vitamin A to reduce lipofuscin accumulation and treat AMD and Stargardt’s diseases. This flawed reasoning applies equally to deuterated vitamin A, which would still be expected to serve as a substrate in the visual cycle, producing both ATR and then A2E.

EX2052 ¶¶243-245; EX2193 ¶¶109-11, 208-227, 229-237; EX1002 ¶242 (“natural property of C₂₀-D₃-all-*trans* retinal that it... forms A2E”).

The Petition provides no rationale for how adding this additional visual cycle substrate would reduce net lipofuscin accumulation that would be generated from both vitamin A already in the body and the added deuterated vitamin A. Instead, Dr. Calman explained that “the more substrate you’re inputting into the

visual cycle, potentially that's *exacerbating* the buildup of ATR, which is the lipofuscin precursor," and "potentially *increase* the buildup of the end product, which in this case is ATR and its harmful lipofuscin products." EX2104, 14:9-16:2. This potential increase in lipofuscin was exactly why vitamin A supplementation was avoided in MD patients. *Id.*

In sum, the art taught that vitamin A deficiency was beneficial for reducing lipofuscin formation associated with macular degeneration and away from adding visual cycle substrate (vitamin A) that could exacerbate lipofuscin accumulation. Petitioner's obviousness allegation disregards the contraindication against administering additional visual cycle substrate.

2. *Ortho* Attributes No Therapeutic Activity to Vitamin A

"[I]t is not enough for [the patent challenger] to merely demonstrate that elements of the claimed invention were independently known in the prior art." *Metalcraft of Mayville, Inc. v. The Toro Co.*, 848 F.3d 1358, 1367 (Fed. Cir. 2017). Yet, at best, the Petition does no more as it fails to demonstrate *why* a POSA would have been motivated to administer *Ortho*'s vitamin A (or *Olson*'s deuterated species) to treat macular degeneration. *In re Gordon*, 733 F.2d 900, 902 (Fed. Cir. 1984) ("The mere fact that the prior art could be so modified would not have made the modification obvious unless the prior art suggested the desirability of the modification.").

All grounds rely on *Ortho* for purportedly “teach[ing] administration of vitamin A in combination with other vitamins and additives to treat and prevent age-related eye diseases, including macular degeneration (as recited in the preamble of claims 28 and 29).” Pet., 40 (citing EX1008). In fact, however, *Ortho* does not teach, suggest, or motivate with a reasonable expectation of success administering an effective amount of vitamin A—deuterated or undertreated—to “retard[] the accumulation of a lipofuscin pigment in a retina” (claim 1) or treat a macular degeneration (claims 28, 29). §V.C.1. Indeed, *Ortho* contains not even a prophetic suggestion with respect to the therapeutic activity of vitamin A. EX2192 ¶¶149-153, 175-179.

The Board should be clear that *Ortho* distinguishes between beta-carotene—provided as an antioxidant—and vitamin A for which it provides no function beyond generically “prevent[ing] deficiencies.” EX1008, [0003]; EX2103, 135:5-16; EX2104, 84:17-85:1, 87:17-89:11 (“I don’t see a specific function listed for vitamin A in” *Ortho*, is not among group of carotenoids). *Ortho*’s vitamin cocktail thus provides no basis to overcome the art’s understanding that vitamin A was ineffective and contraindicated for “retarding the accumulation of a lipofuscin,” treating MD, treating AMD, and treating Stargardt’s. See §V.C.1, *supra*; see also EX2192 ¶¶109-127, 210-222.

The Petition’s assertion that vitamin A was the standard of care for macular degeneration as of 2007 *is false*. EX2192 ¶¶100, 109-127. Vitamin A was never the standard of care. EX2142, 1; EX2140, Table 3; 2144, 1. Supplemental vitamin A was not included in AREDS and was understood to be *undesirable* for macular degeneration, where vitamin A deficiency was recognized to lower lipofuscin formation, and was contraindicated for Stargardt’s patients. EX2156, 3; EX2192 ¶¶59-83, 109-127, 210-222. The AREDS supplement (containing as one component beta-carotene, not vitamin A) had been studied in AMD, but was not standard of care for macular degeneration generally. EX2193 ¶¶95-99. Rather, ***“[m]ost ophthalmologists are reluctant*** to prescribe prophylactic supplementation with high dose antioxidant”—as found in the AREDS beta-carotene, vitamin C, and vitamin E product—for AMD generally. EX1039, 3; *see also* EX2139, 3.

At bottom, the Petition attempts to pluck an undifferentenced vitamin A from *Ortho*’s multi-component cocktail. The Petition then attributes to the undifferentenced vitamin A therapeutic activity to treat macular degeneration that is nowhere suggested much less demonstrated. This illusionary therapeutic activity is inconsistent with repeated studies showing that vitamin A provided no therapeutic benefit and was taught away from for macular degeneration. §V.A.1. The Petition’s rationale is impermissible hindsight at its finest. *KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 421, (2007) (“A factfinder should be aware, of course, of the

distortion caused by hindsight bias and must be cautious of arguments reliant upon *ex post* reasoning.”).

B. A POSA Would Not Have Been Motivated to Administer C₂₀-D₃-Vitamin A To Slow *Mata*’s Hypothetical Pathway

As summarized in the ID,

[t]he Petition, again relying on Dr. Guengerich’s testimony, further explains Mata taught that [1,5] deprotonation at C-20 of retinal — involving cleavage of a carbon-hydrogen bond — was “a pre-requisite for undesirable A2E formation,” and that a skilled artisan “would have recognized that this deprotonation likely was a rate-limiting step in A2E formation” such that slowing the deprotonation “would slow A2E formation,” i.e., lower the production of a toxic reaction product. [Pet.] at 41 (citing EX1002 ¶¶259-260).

ID, 37 (bracketed alternation added); Rehearing (Paper 20), 3-4; Pet., 41-42. The Petition necessarily fails, as Dr. Guengerich abandoned the relied-upon “rate-limiting” argument. Without this premise, the Petition fails to proffer a motivation or reasonable expectation to slow A2E with C₂₀-deuterated vitamin A.

The Petition argues a POSA would have been motivated to use C₂₀-D₃-vitamin A from the POSA:

- First, recognizing the [1,5] shift in *Mata* was “likely a rate-limiting step in A2E formation.”

- Next, knowing that deuterium substitution at vitamin A position C20 (the C-H bond involved in the [1,5] shift) would have been expected to slow A2E formation.

Pet., 41-42 (citing EX1002 ¶¶65-69, 99-123, 145-148, 259-264). This argument, the alleged motivation to combine *Olsen* with *Ortho*, *Widder*, and *Mata*, and the alleged expectation of success in targeting the 1,5 shift all rests Dr. Guengerich's opinion that the 1,5 shift was "likely" rate limiting. *Id.*

Tested at his deposition, Dr. Guengerich abandoned his "likely rate-limiting" argument. Dr. Guengerich's declaration was the Petition's only support for this baseless argument. Stripped of its foundational assumption, the Petition's ancillary arguments based on *Mata*, *Fishkin*⁴, and generic knowledge of deuterium fail to provide any specific motivation for targeting the 1,5 shift. Nor does *Roth*'s study of a gas-phase, concerted 1,5 sigmatropic rearrangement provide any expectation for a similar KIE for the step-wise acid-base tautomerization in the multi-step A2E biosynthetic pathway.

As shown below, the Petition fails to establish a motivation to combine *Ortho* and *Olson* or use C₂₀-D₃-vitamin A to prevent lipofuscin formation or treat macular degeneration.

⁴ EX1011 ("*Fishkin*").

1. Petitioner's Abandoned "Likely" Rate-Limiting Argument

The Petition's assertion that the 1,5 shift would have been recognized as "likely" rate limiting is critical to its case. It necessarily fails as Dr. Guengerich has now disavowed his "rate limiting" opinions.

For motivation, "likely" rate limiting is the *only* tie between *Mata* and the use of deuterium at C20. It is also necessary to Petitioner's expectation of success, since observable KIE is only apparent where the C-H bond breaking is rate limiting. EX2052 ¶¶135-138; *compare* EX1004 ¶101 (KIE where C-H "is involved in the rate-determining step" (quoting EX1047, 3) *with* EX1047, 3 ("An observable isotope effect will *only be apparent*, of course, *where the breaking of a C-H or C-D bond is involved in the rate-determining step.*"). These positions hinge on the Guengerich declaration, as the prior art did not suggest that deuteration at C20 would slow A2E. Pet., 41-42, 67; EX2103, 119:9-17 ("No, I'm not" aware of "anyone prior to the '045 patent suggesting that deuteration of carbon-20 would slow the formation of A2E"). The Petition necessarily fails as Dr. Guengerich has now disavowed his prior "rate-limiting" opinions.

Dr. Guengerich abandoned his argument in full. On cross-examination he admitted that "*I don't think I could say*" that the 1,5 shift was rate limiting. EX2103, 55:3-13. He contradicted his declaration that

It is readily apparent to a person of ordinary skill that *the (1,5)-sigmatropic rearrangement is likely to be the rate-limiting step* in the pathway *because* the kinetics of the (3,3)-sigmatropic rearrangement are significantly faster than that of the (1,5)-sigmatropic rearrangement *the (1,5)-sigmatropic rearrangement would be significantly slower than the (3,3)-sigmatropic rearrangement* (EX1002 ¶178), conceding that “the 3,3-sigmatropic rearrangement or the dimerization process or perhaps even one of the other following the steps then” could be rate-limiting (EX2103, 56:13-23). And, contrary to Petitioner’s claim that “a POSA would have been well aware that the 1,5-sigmatropic shift disclosed in Mata was likely a rate-limiting step” (Pet., 41-42, 67), Dr. Guengerich did not even *“think a POSA is looking for the rate-limiting step in a sequence like this.”* EX2103, 88:12-89:21; 64:15-65:14 (stating that he could not say that which step is rate limiting as “this is difficult research to do”).

Dr. Guengerich retreated to a new argument as this deposition. He now says “it doesn’t necessarily matter what’s rate limiting in the overall process,” that a POSA would not be looking for a rate limiting step, and slowing “any step” would be sufficient. *Id.* This “any step” argument is speculation, not motivation. *In re Stepan Co.*, 868 F.3d 1342, 1347 (Fed. Cir. 2017) (“Reciting Pallas’ teachings that ‘any combination’ of surfactants may be used and that a cloud point above 60°C is desired fails to illuminate why a skilled artisan would have selected the claimed

combination of surfactants and reasonably expected a cloud point above at least 70°C.”); *Duke Univ. v. BioMarin Pharm. Inc.*, 685 F. App’x 967, 978 (Fed. Cir. 2017) (expert testimony suggesting what “could be done” “falls short because it does not address what an ordinary artisan would have done or understood).

Dr. Guengerich’s new argument also contradicts the Petition. Alleged recognition that the 1,5 shift was “likely” rate limiting was the proffered “good reason” to combined *Olson*’s C20-deuterated vitamin A with *Ortho*. Pet., 41, 67. Without with alleged recognition, the Petition fails to show a reason to consider something the art never did, combine *Olsen*’s C₂₀-D₃-vitamin A with *Ortho*, *Mata*, or *Widder*, or a reasonable expectation of slowing of A2E. *Arctic Cat Inc. v. Polaris Industries, Inc.*, 795 Fed. Appx. 827, 833 (Fed. Cir. 2019)(“[T]he Board did not misapply the law by requiring [Petitioner] to prove the facts that it alleged.”).

Stripped of its argument that the [1,5] shift was “likely” rate limiting, the Petition can show neither motivation to administer C20 deuterated vitamin A nor a reasonable expectation that it would retard lipofuscin accumulation or treat MD.⁵

⁵ Dr. Calman’s opinions also fall, as they are likewise premised on “Dr. Guengerich explain[ing] that the deprotonation of C-20 would have been

Pet., 41-42, 45. Indeed, as recognized in denying institution in a prior case involving deuteration, “*the presence of other possible rate-limiting steps*” precludes the Petition from having established an expected KIE as is necessary for its alleged motivation and reasonable expectation of success. *Neptune Generics LLC v. Auspex Pharms., Inc.*, IPR2015-01313, Paper 25, 15 (PTAB Dec. 9, 2015) (denying institution where the effect of deuteration was not predictable “due to the presence of other possible rate-limiting steps”).

2. The Petition Fails to Show the 1,5 Shift Was “Likely” Rate Limiting

A POSA could not have identified the rate-limiting step based merely on inspection of *Mata*’s written chemical reaction scheme, as Dr. Guengerich initially argued. EX2052 ¶¶179-195; EX1002 ¶178. To the contrary, “[a]t the time of the invention, it was not known that [the 1,5 shift was rate limiting].... It was the inventors of the [’045] patent who performed experiments and discovered” it was a valid target for therapy. *Erfindergemeinschaft UroPep GbR v. Eli Lilly & Co.*, 276 F. Supp. 3d 629, 663-64 (E.D. Tex. 2017), *aff’d*, 739 F. App’x 643 (Fed. Cir. 2018) (“Given what was known in the prior art, Lilly did not show that it would

recognized as a rate-limiting step in A2E formation.” EX1004 ¶68 (citing EX1002 ¶98).

have been obvious to consider....”). Dr. Guengerich’s “conclusory expert testimony cannot support an obviousness conclusion.” *Duke*, 685 F. App’x 978-979.

The rate-limiting step is the slowest step in a reaction. EX2052 ¶¶50-53. Determining the rate-limiting factor in a multi-step reaction requires consideration of the relative rates of each step. EX2052 ¶¶183-195. In a complex *in vivo* environment, the rate limiting step can be probed indirectly by the use of inhibitors or deuterium isotope studies—such as those disclosed in the ’045 patent.⁶ EX1014, 3; EX1001, 18:44-21:22. For example, rather than speculating from hypothesized reaction schemes, researchers (after *Mata*) used inhibition assays to identify the rate-limiting step in A2E formation. From these studies they found:

strong evidence that mRPE65 is rate-limiting...in A2E formation
and that mRPE65 is a valid target for therapies designed to prevent the

⁶ The fact “[a]n observable isotope effect will only be apparent, of course, where the breaking of a C-H or C-D bond is involved in the rate-determining step” is what makes KIEs useful in elucidating reaction mechanisms. EX1047, 3 (“The pronounced effects on rates of chemical reactions make deuterium isotope studies a particularly useful tool for elucidating the mechanisms of many reactions of biochemical significance.”); EX2052 ¶¶134-138; EX2103, 127:3-18.

accumulation of lipofuscin and possibly the onset and progression of macular degeneration.

EX2066, 3. By contrast, Petitioner fails to show that the art suggested (or even speculated) that the 1,5 shift in *Mata* was rate limiting. EX2103, 119:9-17.

Petitioner's claim that a POSA could have identified the 1,5 shift as "likely" rate limiting from considering only "Mata's description of the synthetic pathway" is further baseless. *Cf. Pet.*, 67. *Mata*'s chemical reaction scheme is one small part of a much larger process involving countless complex biological and mechanisms. EX2052 ¶¶81-111. These non-chemical processes, such as enzymatic catalysis, transport mechanisms, and lipid bilayer interactions, regulate reaction rates and can themselves be rate-limiting. *E.g.*, EX2052 ¶¶53-54, 81-111, 183-188; EX2066, 9-10. Analyzing a chemical reaction in isolation is meaningless without considering the larger biological context. EX2052 ¶¶183-195.

Dr. Guengerich, however, did not consider biological processes in the formation of A2E, and in several instances was unaware of them:

- He testified that he was "not aware there's any evidence that there is transport or passive defusion [sic] from one compartment in the eye to the next." EX2103, 113:9-114. Such transport discussed throughout the art. EX2052 ¶¶88-97; EX2051, 2, 6; EX2062, 4-6.

- His “rate limiting” opinion is premised on a belief that “enzymatic catalysis was very unlikely because lipofuscin formation was undesirable.” EX1002 ¶98. In fact, the art suggested formation of A2E was enzymatically catalyzed. EX2051, 1, 4-5, 7; EX2073, 3; EX2162, 2.
- He claimed “[t]his reaction also happens very slowly in the eye” [because] “babies generally don’t have macular degeneration; old people do.” EX2103, 70:4-72:7. In addition to the overall accumulation rate being irrelevant to whether the [1,5] shift is slow, Dr. Guengerich apparently fails to understand that Stargardt’s disease—the debilitating disorder that ALK-001 is seeking FDA approval for—commonly afflicts children. EX2192 ¶281.

Considering *Mata* purely “from the perspective of a chemist,” as Dr. Guengerich had, is insufficient. EX1002 ¶98. Having ignored essential biological factors, Petitioner’s argument cannot, even in theory, establish a rate limiting step. EX2052 ¶¶183-195.

Even if a POSA were to guess at a rate-limiting step in *Mata*, the prior art specifically called out other steps as more “likely” candidates. EX2050 ¶¶196-216. Chief amongst these was the biomolecular reaction of NRPE (formed from ATR and PE) and a second molecule of ATR: this was recognized as “*rare*” and “*likely*

to occur infrequently.”⁷ EX1035, 2; EX1034, 2; EX1033, 2; EX2052 ¶¶197-206.

Indeed, ATR was recognized by numerous references, including *Mata*, as rate limiting in A2E formation. EX2052 ¶200; EX1010, 6 (“A2E accumulation should depend on the availability of [ATR]”); EX1036, 2; EX2003, 14. The art’s focus on reducing ATR to inhibit A2E formation was based on this understanding. EX2052 ¶¶112-128, 203-206; EX2003, 35 (explaining that by reducing ATR with visual cycle inhibitors reduced the “probability of the secondary condensation reaction”); EX2063, 1, 5.

In contrast to the literature describing other steps as “rare” and “slow,” the Petition identifies no art suggesting that the 1,5 shift was likely rate-limiting. EX2103, 119:9-17 (“No, I’m not” aware of “anyone prior to the ’045 patent suggesting that deuteration of carbon-20 would slow the formation of A2E”); EX2052 ¶¶217-220. No prior art interpreted *Mata* as suggesting the 1,5 shift was rate limiting. EX2052 ¶¶221-230 Dr. Guengerich acknowledged that nothing in

⁷ The art also described the acid hydrolysis of A2PE to A2E as occurring “very slowly.” EX2051, 4, 7; EX2073, 3; EX2052 ¶¶207-211. Phagocytosis too, would have been recognized as more likely rate-limiting than the 1,5 shift.

EX2052 ¶¶207-216; EX2069, 8; EX2080, 1.

Petitioner's key *Mata* and *Fishkin* references suggested the 1,5 shift was rate limiting. EX2103, 121:6-124:4.

Dr. Guengerich's testimony that C-H bond breaking "would already have been relatively slow under physiological conditions" is also contradicted by his own 2005 publication in which he recognized "a tendency [in the literature] *to regard C–H bond breaking as generally being relatively rapid.*" EX1002 ¶¶98; EX2083, 1. Dr. Guengerich's own view on this did not change until 2012—years after the '045 patent's priority date. EX2009, 199:4-201:5.

In the absence of prior art, Dr. Guengerich resorted to hindsight. *Orexo AB v. Actavis Elizabeth LLC*, 903 F.3d 1265, 1272 (Fed. Cir. 2018) (affirming finding of non-obviousness where expert's reasoning was "hindsight bias" that "recreate[d] the prior art from the teaching in the [asserted] Patent"). He argued that "the patent" and a "subsequent paper" showed the overall formation of A2E "took a long" time. EX2103, 120:6-19, 123:8-124:4, ("the authors were thinking about this because they came up with the patent the next year or two then");⁸ *see also* EX1002 ¶¶98, 184, 266 ("reasonable expectation of success is confirmed by the

⁸ Dr. Guengerich also confuses the authors of *Fishkin* from Columbia University with the inventor Dr. Washington, also from Columbia University. EX, 1011, 1; EX1001, cover.

'045 patent"). The Petition similarly relies—improperly—on the inventor's discovery to argue a reasonable expectation of success. Pet., 45-46 ("The '045 patent further admits that C20-deuterated retinoids" retards lipofuscin pigments.); ID, 35, n.17.

In sum, the critical "likely" rate-limiting thread tying the Petition together is utterly meritless. The theory lacks support from the art, relying instead on Dr. Guengerich's speculative *ipse dixit*, which he has since abandoned. The Petition cannot survive without its core argument that— "as Dr. Guengerich explains"— "a POSA would have recognized that this deprotonation [1,5 shift] likely was a rate limiting step in A2E." Pet., 41.

3. The Petition's Ancillary Arguments Fail to Establish A Motivation

Stripped of its now-abandoned rate-limiting argument, the Petition's ancillary arguments fail to establish any specific motivation to administer C₂₀-D₃-vitamin A. *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1365 (Fed. Cir. 2007) (reasonable expectation of success not shown by "try[ing] each of numerous possible choices until one possibly arrived at a successful result") (citations, quotations omitted); *Medit Corporation v. 3Shape A/S*, IPR2023-01316, Paper 6 at 30-31 (PTAB Mar. 29, 2024) (denying institution where "[n]either Petitioner nor

Dr. Liang explains how one of ordinary skill in the art would have been *led or motivated to select the particular combination*) (citing *Pfizer*, 408 F.3d at 1365).

a. *Mata and Fishkin Do Not Suggest Targeting the 1,5 Shift Specifically*

Nothing in *Mata* or *Fishkin* directed one towards the 1,5 shift. EX2103 121:6-124:4; *see also id.*, 119:9-17; *cf. Pet.*, 40-42. “Given what was known in the art,” targeting the 1,5 shift would not have been obvious from their non-specific disclosures. *UroPep*, 276 F. Supp. 3d at 663-64. (“Given what was known in the prior art, Lilly did not show that it would have been obvious to consider....”).

First, Petitioner’s assertion that the C-20 bond breaking is a “prerequisite” to A2E formation does not motivate targeting the 1,5 shift. *Pet.*, 13, 36-37. *All* of the steps in *Mata*’s pathway are similarly “prerequisite.” EX2052 ¶¶175-178. Dr. Guengerich’s upstream/downstream argument fails for the same reason. EX1002 ¶98; EX2052 ¶¶172-174. These generic disclosures do not suggest using C₂₀-D₃-vitamin A to target the 1,5 shift specifically. *Pfizer*, 480 F.3d at 1365.

Second, *Mata*’s concluding statement that “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway *may* thus *be* an effective treatment strategy” is equally non-specific to any of the “one or more steps.” *Pet.*, 30 (citing EX1010, 6); *id.*, 2, 40, 42. This “speculative and tentative disclosure of what ‘might’ or ‘may’ lead [a desirable result] does not sufficiently direct or instruct one

of skill in this art.” *Star Sci., Inc. v. R.J. Reynolds Tobacco Co.*, 655 F.3d 1364, 1376 (Fed. Cir. 2011). Moreover, a POSA would not understand “pharmacological inhibition” as suggesting deuterium substitution, much less suggest adding *more* precursor for ATR. EX2052 ¶¶165-171; EX2192 ¶¶180-183; §V.A.I, *supra*.

b. General Deuterium Disclosures Provide No Specific Motivation

Petitioner argues motivation from deuterium’s “known” potential to “slow undesirable reaction” and a “significant interest” in creating deuterated drugs. Pet., 2, 7, 15 (citing EX1002 ¶123); EX1004 ¶¶96-102. But without first recognizing the C-H step was rate limiting, a POSA could not have expected any effect from deuteration or had Petitioner’s motivation to combine *Olsen*’s deuterated vitamin A with *Ortho*, *Mata*, or *Widder*.⁹ Pet., 40-43; EX2052 ¶¶135-136; *BioMarin*, 685 F. App’x at 977-979 (“the evidence of record does not establish the conditions precedent” to consider the specific treatment). Nor can generic deuterium chemistry concepts provide the requisite specific motivation. *Genetics Inst., LLC v.*

⁹ Whether “a” or “the” rate limiting step, the C-H bond must be rate limiting according to the Petition. Pet., 40-42, 67; EX1002 ¶¶98, 107-108, 178, 181, 184, 260, 262, 351, 353; EX1047, 3. But the Petition has not established the 1,5 shift to be either “a” or “the” rate limiting step. §V.B.1-2, *supra*.

Novartis Vaccines and Diagnostics, Inc., 655 F.3d 1291, 1306 (Fed. Cir. 2011)

(general motivation “to make smaller, truncated proteins to solve the cloning difficulties... would not have supplied researchers with a reason to make the group of proteins claimed”); *UroPep*, 276 F. Supp. 3d at 663-64; *BioMarin*, 685 F. App’x at 978; ID, 37.

First, the ’045 patent’s use of deuterated vitamin A is fundamentally different than the prior art’s limited therapeutic applications of deuterium substitution. EX2052 ¶¶233-252. Prior attempts at therapeutic use were narrowly focused on improving existing drugs for their intended purposes. EX2052 ¶¶139-157. In contrast, the ’045 patent uses deuterium to create an entirely new treatment to retard lipofuscin accumulation *the opposite* of vitamin A natural effect. §V.A.1, *supra*. These are fundamentally different strategies. EX2052 ¶¶233-237.

Second, the prior art does not support Petitioner’s alleged “known” potential for generically slowing *any* “undesirable reaction[s].” *Cf.* Pet., 7-8, 15. Deuterium substitution was used only in “highly specific situations” to slow or redirect enzymatic metabolism. EX2076, 7; *see* EX1012, 6; EX1046, 5-6 (“Resistance to [enzyme] P450-induced changes may lead to an increase in duration of pharmacological action.”); EX1051, 5 (“conservative strategy... on carbon atoms susceptible to the cytochrome P-450 oxidation”). Petitioner does not identify a single analogous attempt to use deuterium to create a novel intervention, as is the

case here. EX2052 ¶¶239-252; EX2104, 55:3-71:6 (identifying uses of deuterium to inhibit metabolism of known drugs).

Finally, there was no “significant interest” in even these narrow uses for deuterium substitution. EX1004 ¶¶96-102. EX1013, 41; EX2076, 7. Petitioner relies on Dr. Calman, a general practice ophthalmologist not qualified to offer this opinion on the subject. EX1005, 1-15; EX2104, 60:4-62:3 (“defer to Dr. Guengerich”), 62:4-63:8 (“defer”), 70:23-71:6 (“defer”), 76:7-78:1 (“defer”, “I have never worked independently with deuterated compounds”), 99:15:100:4 (“defer”); §II.B.1, *supra*. In contrast, Dr. Guengerich makes no mention of using it therapeutically much less a “significant interest” therein. *See* EX1002 ¶11; *compare* EX1002 ¶¶99-123 (deuterium background) *with* EX1004 ¶¶96-102 (Dr. Calman “significant interest”). Nor could he, given his prior testimony relying on “activity between about 2007 and 2012” to assert “site-selective deuteration of known compounds was a popular and potentially lucrative area” *as of 2012*—years the ’045 patent’s priority. EX2008 ¶¶59-62. Neither expert identifies anything in the prior art, which consistently describes the therapeutic use of deuterium as “speculative” and “not expected to be an effective strategy.” EX1013, 41; EX2076, 7.

Petitioner cannot provide a motivation to use deuterium without the assumption that the 1,5 shift was rate limiting on A2E formation. Petitioner cannot

backfill this missing motivation with limited prior art attempts to improve enzymatic metabolism, a fundamentally different purpose than the novel therapeutic use of deuterium in the '045 patent.

c. *Roth and Ito* Provide Neither an Expectation of a Large KIE nor a Motivation to Target the 1,5 Shift

Roth and *Ito*¹⁰ do not provide a motivation to target the 1,5 shift in the multi-step A2E pathway or a reasonable expectation of a large KIE therefore. Their single step reaction mechanism is distinct from the 1,5 reaction in the A2E pathway 1,5 shift and reveals nothing about its rate relative to other steps in this complex biosynthesis.

First, the Petition argues that *Roth*'s large KIE would have motivated using deuterium to slow lipofuscin accumulation in *Mata*'s A2E pathway based on an expectation of a similar KIE. Pet., 42, 67. But the concerted mechanism of *Roth*'s 1,5 sigmatropic rearrangement with pentadiene is fundamentally different from and no way predictive of the NRPE's 1,5 mechanisms in the A2E pathway.

EX2052 ¶¶268-281. Dr. Guengerich's only justification for relying on *Roth*—that

¹⁰ *Ito* (EX1016) relies on the same *KIE* reported by *Roth* (EX1015). EX2052 ¶¶253-258.

it shares the same reaction mechanism as the A2E pathway 1,5 shift (EX1002 ¶¶93-94, 98, 116-122, 178)—is fundamentally mistaken.

A POSA would have understood the 1,5 mechanism in the A2E pathway to be a relatively fast, acid-base *tautomerization*. EX2077, 3. EX2052 ¶¶272-279. This is reflected in the record evidence, which consistently describes it as a tautomerization—the only exception being *Mata*. EX2052 ¶¶277. Petitioner’s key *Fishkin* reference, for example, identifies it as an acid-base tautomerization to explain the reaction mechanism. EX2052 ¶¶282-283. Direct experiments on retinoids under aqueous conditions empirically concluded the same. EX2052 ¶¶278-281, 284-294; EX2077, 1 (“13-*cis*-retinylidene-*n*-butylamine was shown to undergo thermodynamic equilibration with the trans isomer by general base catalysis”), 3 (Fig. 5, discussion); EX2078, 1 (“Under the basic conditions provided by the sodium hydride, one of the relative acidic C20-methyl protons is abstracted by the strong base.”), 2 (Scheme 1). Notably, base catalysis is not possible under *Roth*’s gas phase conditions but does occur in aqueous and *in vivo* systems. EX2052 ¶¶284-294. Tautomerization of NRPE is distinct from *Roth*’s 1,5 sigmatropic rearrangement, which proceeds via concerted (simultaneous) bond breaking and formation with any intermediates. EX2052 ¶¶272-276; EX2045, 315.

Dr. Guengerich reliance on the wrong mechanism in *Roth* guts his opinion, which necessarily depends on considering the *correct* reaction mechanism. As Dr. Guengerich explains:

- “You know, one has to consider the mechanism of how you’re doing that” (EX2103, 129:9-20)
- “And different types of reactions that occur by entirely different mechanisms, so one doesn’t—cannot—well, you have to consider each one individually or at least in terms of class mechanism.” (*id.*, 128:20-129:7);
- “My answer is the same. It depends on the mechanism. Here we have in 1,5-sigmatropic rearrangement, we have a concerted synchronous mechanism which is consistent with a high kinetic isotope effect”(*id.*, 130:19-131:12);
- “That depends on the mechanism” (*id.*, 131:14-24).

Second, even if the mechanisms were the same, *Roth*’s gas phase cis-pentadiene KIE would have been relied upon to reasonably predict a KIE for NRPE in the A2E pathway. EX2052 ¶¶295-298. *Roth*’s large KIE is property of the highly symmetric cis-pentadiene hydrocarbon—*Roth*’s reason for selecting cis-pentadiene in the first place. EX1015, 3-4; EX2052 ¶¶296-297. By contrast, NRPE is a large, complex, and highly asymmetric heteromeric molecule with different

potential electronic resulting from the involvement of nitrogen in the 1,5 shift.

EX2052 ¶298. At best, only a small *intrinsic* effect would be expected for a non-symmetrical transition state. EX1015, 3-5; EX2052 ¶132.

Finally, the Petition also rests on the fallacy that because the 1,5 shift was slow in *Roth* therefore it is “likely” rate limiting in Mata’s A2E pathway. Pet., 41-42, 67; EX1002 ¶¶178, 259-261; EX2103, 59:11-25, 62:3-8.

To be clear: *Roth* is a single step reaction. EX2103, 61:11-62:8. (“It’s the only step. It’s a single reaction, yes”); EX2052 ¶¶259-267. Even if it were the same mechanism (it is not) and a comparable molecule (it is not), *Roth*’s single step provides no indication that C-H bond breaking is rate limiting in the multi-step A2E biosynthesis. EX2103, 62:10-23 (“Q: Roth doesn’t tell you whether sigmatropic shift in a different multistep sequence is going to be overall rate limiting, correct? *A: It does not*”).

Roth measured the *intrinsic* isotope effect for a single reaction: 1,5 sigmatropic rearrangement. EX1015, 6, n. 11; EX2052 ¶¶259-261. An intrinsic isotope effect measures the impact of deuterium on this single step. Conversely, an *observed* isotope effect reflects deuterium’s impact on the overall reaction rate (in this case, A2E formation). EX2052 ¶¶135-138. An *intrinsic* effect does not reasonably predict an *observed* effect (much less its magnitude) in a multi-step process (as in A2E formation) because other steps in the reaction can “mask” the

impact of the single step. EX2085, 1, 7; EX2083, 1; EX2084, 3; EX1013, 34; EX2052 ¶262.

Thus, the Petition lacks any basis to rely on *Roth*'s concerted single step, gas phase 1,5 sigmatropic rearrangement to targeting the 1,5 shift in the complex A2E biosynthesis or reasonably expect a large KIE.

C. No Reasonable Expectation of Success

The Petition failed to establish a reasonable expectation of success of administering an “effective amount” to “retard[] the accumulation of a lipofuscin pigment in a retina” (claim 1) or to “treat[] a macular degeneration” (claims 28, 29) for any ground. *Eli Lilly*, 8 F.4th at 1344 (Patent challenger failed to prove claimed “effective amount”).

1. “Effective Amount” Not Reasonably Expected

First, failing to demonstrate that the “effective amount” limitations are even taught or suggested, the Petition addresses none with particularity. *Adaptics Ltd. v. Perfect Co.*, Case IPR2018-01596, Paper 20 (PTAB March 6, 2019) (informative) (petition must identify the grounds with particularity); *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); 35 U.S.C. § 312(a)(3). They are addressed only in passing for claims 28-39 and not at all for claim 1. *See* Pet., 1 (passing reference), 4 (unsupported “effective amount” assertion not linked to claimed methods), 25 (same), 29-31 (citing back to claims 28 and 29 without

addressing claim 1 “effective amount” limitation). Nor does the desirability of retarding lipofuscin accumulation or treating MD establish the claimed “effective amount.” *Abbott Laboratories v. Sandoz, Inc.*, 544 F.3d 1341, 1352 (Fed. Cir. 2008) (“[K]nowledge of the goal does not render its achievement obvious.”).

At most, the Petition argues that *Ortho* “teaches administering a vitamin A-containing product to individuals to treat or prevent age-related eye diseases including” AMD and that “the composition comprises an effective amount of vitamin A together with other vitamins (e.g., C, D, and E) and minerals (e.g., zinc). . . .” Pet., 25. *Ortho*, however, attributes no therapeutic efficacy to vitamin A (beyond as a nutritional supplement cocktail) and provides no guidance on an “effective amount” of vitamin A for “retarding the accumulation of a lipofuscin pigment in a retina” or treating MD.¹¹

The Petition does not (and could not) assert that its other ground reference (*Olson, Mata, and/or Widder*) overcomes this deficiency. No therapeutic purpose

¹¹ *Ortho* distinguishes vitamin A from antioxidant carotenoids (e.g. beta-carotene) and does not even assert that antioxidants retard lipofuscin formation. EX1008, [0001], [0003], [0006], [0008]-[0009]; EX2192 ¶¶109-111, 175-179; EX2104, 33:5-20, 34:3-10; EX2103, 135:5-138:22. 155:2-16; Pet., 1 (“nutritional supplement”); EX1004 ¶177 (“for nutritional and health benefits”).

or effect of C₂₀-deuterated vitamin A is taught or suggested by *Olson*. EX2104. 131:21-132:4 (“used as a tracer”), 137:24-138:13 (“isotope dilution studies”), 139:21-140:3 (not “about treating a disease”). And neither *Mata* nor *Widder* are relied upon to teach or suggest any effective amount of vitamin A, which is “diametric opposed” to their common premise. *E.g.*, Pet., 15-19; EX2103, 172:23-177:20; §V.A.1.

Second, Petitioner’s rationale that the elementary components were known and some taught “to treat or prevent eye diseases such as macular degeneration, including as a nutritional supplement” (Pet., 43-44) provides no basis for a reasonable expectation of achieving the claimed “effective amount[s].”¹² *Eli Lilly*, 8 F.4th at 1344. Where the art recognized that administering vitamin A could lead to more lipofuscin formation (§V.A.1), Petitioner provides no basis to reasonably expect that any amount of vitamin A would be an *effective amount* to retard lipofuscin accumulation (claim 1) or treat MD (claims 1, 28, 29).

¹² Petitioner’s assertion that “it was well-known by 2007 to administer vitamin A to a subject to treat or prevent eye diseases such as dry, age-related macular degeneration” (Pet., 1, 4, 25) is demonstrably wrong. EX2192 ¶¶109-127, 210-222; §V.A.1.

Third, the long-felt need and failures of others to develop MD treatments reinforces the Petition’s failure to establish a reasonable expectation of success for the claimed “effective amount.” See §§V.A.1, V.D; *U. of Strathclyde v. Clear-Vu Lighting LLC*, 17 F.4th 155, 165 (Fed. Cir. 2021) (“[W]here the prior art evidences only failures to achieve that at which the inventors succeeded, no reasonable fact finder could find an expectation of success based on the teachings of that *same* prior art.”).

All told, adding more substrate to the visual cycle, as proposed by the Petition based on *Ortho*, could only have been expected to increase lipofuscin and aggravate MD. The Petition’s asserted references and declarants thus fail to establish a reasonable expectation of success for the claimed “effective amount” to “retard[] the accumulation of a lipofuscin pigment in a retina” (claim 1) or to “treat[] a macular degeneration” (claims 28, 29).

2. Petitioner’s Ancillary Arguments Fail

Petitioner’s remaining assertions (Pet., 42-43, ID 34-35) further fail to support a reasonable expectation of success.

First, disclosures of (1) deuterated vitamin A species as a biological tracer and (2) pharmaceutically acceptable carriers and formulations (Pet., 43-44) do not support a reasonable expectation of efficacy to retard lipofuscin accumulation or treat MD, including dry-AMD and Stargardt’s disease. *Unigene Labs., Inc. v.*

Apotex Inc., 655 F.3d 1352, 1360 (Fed. Cir. 2011) (“Obviousness requires more than a mere showing that the prior art includes separate references covering each separate limitation in a claim under examination.”).

Second, desirability of reducing lipofuscin formation, non-specific speculation about what “*may... be* an effective,” identification of “pre-requisites,” and reliance on the patent’s own disclosures for the properties of C20-deuterated retinoids do not speak to a POSA’s reasonable expectation of success of retarding lipofuscin or treating MD. Pet., 42-46; §§V.B.2, 3.a, *supra*.

Finally, *Roth* and *Itou* are directed to the *intrinsic* isotope effect of materially different reaction (concerted sigmatropic rearrangement) of a different compound (pentadiene) in a different environment (gas phase). They fail to support a reasonable expectation of achieving a similar *observed* isotope effect, much less 5-10 times slowing (Pet., 55) in the multi-step biosynthesis of A2E or that deuterated vitamin A will retard lipofuscin accumulation or treat MD, including dry-AMD and Stargardt’s disease. Pet., 44-45; §V.B.3, *supra*.

D. Long-Felt Need, Failure of Others, and Unexpected Results Support the Non-Obviousness of the ’045 Patent

“Objective evidence... can protect against the prejudice of hindsight bias, which often overlooks that the genius of invention is often a combination of known elements which in hindsight seems preordained.” *Power Integrations, Inc. v.*

Fairchild Semiconductor Int'l, Inc., 711 F.3d 1348, 1368 (Fed. Cir. 2013) (cleaned up). Here, the long-felt need, failure of others, unexpected results, and praise demonstrate nonobviousness.

1. Long-Felt But Unmet Need For The Treating Macular Degeneration That Others Tried But Failed To Satisfy

As of 2007, there was a long-recognized unmet need for treatments to slow the progression of macular degeneration resulting from lipofuscin accumulation—including for dry AMD and Stargardt’s disease—*without* inducing visual impairment such as night blindness or impaired dark adaptation. EX2192 ¶¶55, 70, 74, 284, 290-91, 309, 314; EX1004 ¶144; *Apple Inc. v. Samsung Electronics Co., Ltd.*, 839 F.3d 1034, 1056, (Fed. Cir. 2016) (*en banc*). No such treatments were then available. EX2139, 1; EX2141, 1; EX1039, 4; EX2111, 1; EX2136, 1; EX2161, 1.

The need was substantial given that, for example, AMD “is the leading cause of blindness” in older adults. EX1039, 1; EX2192 ¶90; EX2136, 1. Stargardt’s disease—the most common form of inherited juvenile macular degeneration—causes blindness in children and has “a severe and devastating impact on daily life.” EX2149, 6; *see also* EX2148, 1; EX2146, 1; EX2172, 1; EX2173; EX2134; EX2135; EX2149.

The absence of treatments to slow the progression of macular degeneration was not for lack of trying. This was an area of intense research where many had tried and failed. EX2191 ¶¶101-102, 275-277, 281-288; EX2052 ¶¶300-306; EX2103, 170:25-171:14; EX2058, 4. The problem was that “[m]acular degeneration falls into a class of diseases that are generally considered difficult therapeutic targets.” EX2074, 11. As the FDA explained, “Developing a treatment for a rare disease can be especially challenging.” EX2189 (awarding grant for ALK-001); EX2188 (awarding grant for ALK-001). In this context, that vitamin A had been tested and found ineffective (EX2192 ¶283; EX2151, 1) and that deuterated vitamin A (*Olson*) was long known but not applied to retard lipofuscin accumulation or treat MD indicates that Petitioner “only traverses the obstacles to this inventive enterprise with a resort to hindsight.” *Leo Pharm. Prods., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013); *In re Wright*, 569 F.2d 1124, 1127 (CCPA 1977) (“age of the references” relevant where “the art tried and failed to solve the problem”); *Orexo*, 903 F.3d at 1273 (Fed. Cir. 2018) (“Despite the extensive study, this improvement over the then-available treatments... is not proposed or suggested in the references.”); ID, 41.

2. Alkeus's ALK-001 For the Treatment of AMD and Stargardt's Disease Meets the Long-Felt Need

Alkeus is developing a deuterated vitamin A known as ALK-001, specifically C20-D3-retinyl acetate (gildeuretinol). EX2191 ¶¶8-12; EX2086; EX2087; EX2088; EX2089; EX2090; EX2091; EX2092; EX2093; EX2094; EX2095; EX2096; EX2097; EX2098; EX2099; EX2100; EX2101; EX2102. The FDA has awarded ALK-001 Orphan Drug Designation and Breakthrough Therapy Designation for the treatment of Stargardt's disease. EX2096; EX2191 ¶¶50-51. The use of ALK-001 in the treatment of macular degeneration, including the "TEASE" clinical trials for Stargardt's disease and "SAGA" trial for Geographic Atrophy (GA) (an advanced form of dry AMD) practices at least claims 1, 2, 4-15, 18, 19, 26, 28-30, 32-42, 45, 46, 53 of the '045 patent. EX2192 ¶¶264-270.

The completed TEASE-1 study showed that ALK-001 slowed the growth of retinal atrophy (area of damage to the retina) by 21% with no reports of night blindness or delayed dark adaption. EX2088, 2; EX2089; EX2090, 1-2; EX2191 ¶¶15-29; EX2192 ¶¶289-291. These outcomes "represent the first time that a therapeutic intervention slows the progression of STGD1 in a clinically and statistically meaningful way." EX2088, 2. TEASE specifically practices at least claims 1, 2, 4, 11-15, 18, 19, 26, 28-30, 38-42, 45, 46, 53 of the '045 patent. EX2192 ¶¶266-270.

Interim TEASE-3 data further show that ALK-001 “arrested vision loss and the progression of retinal pathology” in patients with presymptomatic Stargardt’s disease. EX2091, 2; *see also* EX2092, 1; EX2191 ¶¶30-38; EX2192 ¶¶292-293. After up to 4 years treatment, these patients have remained asymptomatic with no disease progression and without adverse reactions or safety concerns. EX2092, 1; *see also* EX2091, 2-3.

The demonstrated efficacy of ALK-001 in Stargardt’s reflects that it will also be effective in macular degeneration generally as they share the common pathophysiology of toxic lipofuscin accumulation, with Stargardt’s being an accelerated extreme. EX2192 ¶¶103, 294. This is confirmed by the efficacy of ALK-001 in SAGA for patients with geographic atrophy, an advanced form of dry AMD. EX2192 ¶¶278-280.

Specifically, in the Phase 3 SAGA study of ALK-001 for GA, treatment with ALK-001 “was associated with slower growth of [geographic atrophy] lesions and improved visual acuity” and significantly less loss of low luminance visual acuity. *See* EX2099; EX2095; EX2094; EX2191 ¶¶39-49. This study specifically practices at least claims 1, 2, 4-10, 19, 26, 28-30, 32-37, 46, 53 of the ’045 patent. EX2192 ¶¶266-270. Since geographic atrophy is the advanced form of dry AMD, the SAGA results again reflect that ALK-001 will treat less severe or advanced macular degenerations. EX2192 ¶¶274-275.

3. Alkeus's ALK-001 Overcame Skepticism and Was Widely Praised

ALK-001 for the treatment of MD has received significant praise and recognition. *Institut Pasteur & Universite Pierre Et Marie Curie v. Focarino*, 738 F.3d 1337, 1347 (Fed. Cir. 2013) (“industry praise... provides probative and cogent evidence”). It further overcame skepticism. *In re Dow Chemical Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (“[t]he skepticism of an expert, expressed before these inventors proved him wrong, is entitled to fair evidentiary weight”).

Regarding skepticisms, there were concerns that administering deuterated vitamin A would not be effective. EX2192 ¶¶300-303; EX2180, 14; *see also* EX2179, 3; EX2161, 9. There were further concerns because “there [were] very few reports of deuterated derivatives being used as bona fide drug treatments.” EX2161, 9.

ALK-001 has overcome this skepticism. This is reflected in FDA Breakthrough Therapy Designation, which is based on “preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s).” EX2107, 1. ALK-001 has also been praised as “a **groundbreaking** event in” Stargardt’s disease, which “until now would progress unrelentingly to vision loss and blindness because of buildup of material in the retina....” EX2182, 1; EX2092, 1. (“The dramatic delay of vision

and photoreceptor loss in this small cohort [as] an *exciting advancement* in the therapy for ABCA4-related Stargardt’s disease....”).

As documented in a 2022 FDA hosted a Patient Listening Session for Stargardt’s Disease, praise has also come from patients, families, and ophthalmologist. *See* EX2183; EX2149. One patient described ALK-001 “as giving her the ability to enjoy her passions again, hope for her disease to stop progressing, and hope for future restoration of her vision.” EX2149, 14. And one parent reported that when she “inquired about the clinical trials available” for her daughter, “[e]very doctor responded that in their opinion, should the patient be their child, that they would choose the oral investigational drug ALK-001 for their family.” *Id.*, 15, 19 (ALK-001 clinical trial recommended by ophthalmologist who “would have her own children participate in it”).

Even before these clinical results were available, the invention received praise from Dr. Guengerich based on its pre-clinical results. As an editor at the Journal of Biochemistry in 2010, Dr. Guengerich reviewed two of Dr. Washington’s publications described his invention. On behalf of the journal, Dr. Guengerich and his reviewers described one as “*an innovative paper* on the use of deuterium in vitamin A to provide a significant kinetic isotope effect to slow down the rate of dimerization of retinaldehyde that leads to the production of ATR

dimer, which is associated with the onset of macular degeneration.” EX2056, 1.

They called the other’s use of deuterated vitamin A “*quite novel*.” EX2057, 1-2.

4. Unexpected Results of the Claimed Method

Evidencing its nonobviousness, the use of C20-deuterated vitamin A according to the claimed methods has the surprising ability to reduce lipofuscin accumulation, and thereby treat macular degeneration, without inducing night blindness or impaired dark adaptation. EX2192 ¶¶304-317; *In re Soni*, 54 F.3d 746, 750 (Fed. Cir. 1995).

For example, the ’045 patent specification and Kaufman 2011 (EX2006) demonstrate that, unlike visual cycle antagonists (e.g., fenretinide, TBH), C20-deuterated vitamin A reduced lipofuscin pigments and deposits without impeding the visual cycle. EX1001, 3:25-27, 7:12-24, 20:60-21:22 (Example 6), 7:32-36, Fig. 7; EX2006, 1. As the patent explains, via the inventive methods “many of the disadvantages, such as, delayed dark adaptation, unformed visual pigment, which can lead[] to vision impairment and loss, high drug doses, and the potentially adverse side effects of prior methods are avoided.” EX1001, 7:32-36. This is surprising given the state of the art where prior (and even other current) attempts are premised on visual cycle impairment, which can lead to night blindness and impaired dark adaptation. EX2192 ¶¶70, 74, 314; EX1001, 3:38-40 (“One

immediate disadvantage of slowing the visual cycle is that it leads to delayed dark adaptation and poor vision in dim light or at night.”).

The efficacy of ALK-001 in the TEASE and SAGA trials without inducing night blindness or impaired dark adaption would also have been unexpected, as reflected in the skepticism and failures discussed above. §V.D1-3, *supra*. Indeed, in clinical trials there were “no difference[s] in dark adaptation parameters between gildeuretinol-treated and placebo cohorts (Table 1), despite plasma retinol being approximately 10% that of normal levels in the gildeuretinol cohort, normally defined as severe vitamin A deficiency.” EX2090, 2; EX2088, 2; EX2091, 1. While confirmatory of the pre-clinical studies in the '045 patent specification and Kaufman 2011 (EX2006), these clinical results are unprecedented and contrary to the expectation that visual side effect were unavoidable when attempting to reduce treat macular degeneration by retarding lipofuscin accumulation. EX2192 ¶¶70, 74, 314.

Another unexpected result was that ALK-001 was found to quickly replace normal vitamin A stores. *E.g.*, EX2090, 1 (“At the 8-week pharmacokinetic analysis, 87% and 92% of plasma vitamin A was in the form of [C20D₃-vitamin A] in the 14 and 24 mg cohorts, respectively.”); EX2088, 2 (“On average, ~90% of vitamin A was replaced with deuterated vitamin A, which was maintained over time.”); EX2181, 1; EX2192 ¶302.

In sum, the claimed method enables effectively retarding lipofuscin accumulation and treating MD without the visual side effects attendant to lowering vitamin A. EX1001, 20:60-21:22, Fig. 7; EX2006, 2-3. This is contrary to what would have been expected from prior art attempts, where reducing lipofuscin pigments and impeding the visual cycle were inseparable. *See, e.g.*, EX1001, 3:38-4:41; EX1031, 171, 222-224, 227.

E. Additional Deficiencies of Ground 1 (Ortho Pharma and Olson 1988): Claims 1-9, 19-23, 25-26, 28-36, 46-50, and 52-53

1. No Motivation to Combine with a Reasonable Expectation of Success

Ortho and *Olson* are addressed to entirely different purposes. *Ortho* describes a nutrient supplement cocktail containing, but attributing no therapeutic activity to, vitamin A. §V.A.2, *supra*. *Olson*, by contrast, provides the synthesis of deuterated vitamin A at most for non-therapeutic studies. EX1006, 1. The Petition fails to establish a motivation to combine, much less a reasonable expectation of success, in view of these differences. *Knauf Insulation, Inc. v. Rockwool Intl. A/S*, 788 Fed. Appx. 728, 730 (Fed. Cir. 2019) (“substantial evidence does not support the combination of references relied on by the Board solely based on the similarity of their disclosed reactions”).

The Petition’s argument for combining *Ortho* and *Olson* rests entirely on Dr. Guengerich’s now abandoned and baseless “likely” rate limiting argument. *See*

Pet., 41-42, 67; *see* §V.B, *supra*. Petitioner’s “case was doomed when it failed to prove the premise it offered for combining” *Ortho* and *Olson*. *Arctic Cat Inc. v. Polaris Industries, Inc.*, 795 Fed. Appx. 827, 833 (Fed. Cir. 2019) (“[T]he Board did not misapply the law by requiring [Petitioner] to prove the facts that it alleged.”).

2. Retarding the Accumulation of a Lipofuscin Pigment (claims 1 and 2-9, 19-23, 25-26)

Petitioner argues that “Ortho Pharma teaches administering a vitamin A-containing composition to treat or prevent eye diseases such as age-related macular degeneration, and Olson 1988 teaches claimed C₂₀-deuterated vitamin A.” Pet., 30. This does not, however, even purport to address—as a teaching, suggestion, motivation, or reasonable expectation of success—“retarding the accumulation of a lipofuscin pigment in a retina” as recited in claim 1 and its dependents.

EX2192 ¶¶175-179, 193-207; §V.A, *supra*; 35 U.S.C. § 312(a)(3).

To the contrary, *Ortho* at most teaches vitamin A to address dietary deficiencies whereas the art, by contrast, recognized that vitamin A supplements lacked benefit and risked *accelerating* the accumulation of a lipofuscin pigment in the retina. §V.A.1, *supra*. That is, *Ortho* would be understood to teach the opposite of “retarding the accumulation of a lipofuscin pigment in a retina.” And neither

Ortho nor *Olson* teach or suggest any therapeutic use of amount of any deuterated vitamin A. EX2192 ¶¶149-155, 175-179.

3. MD (claims 4, 28, 29-31, 46-50, 52-53) and AMD (5-9, 32-36)

The Petition fails to establish that *Ortho* and *Olson* teach the claimed “effective amount” of vitamin A (or deuterated vitamin A) for treatment of MD or AMD. §V.E.1. Objective indicia further render these claims non-obvious. §V.D.

4. Forms A2E *in vitro* About 7 Times Slower (claim 9, 36, 53)

The Petition fails to show a teaching, suggestion, or motivation with a reasonable expectation of success for the claimed 7x slowing of A2E, which is a large *observed* KIE. EX2083, 1, 9-10. Petitioner’s misplaced reliance on *Roth*’s *intrinsic* KIE for an entirely different reaction fails to establish any expectation of the claimed 7x *observed* KIE. § V.B.3.C. Indeed, *observed* isotope effect “was invariably found to be much smaller” than the intrinsic isotope effect. EX2085, 1.

F. Additional Deficiencies of Ground 2 (Ground 1 in Further View of *Mata*): Ground 1 + Claims 10-15, 18, 37-42, and 45

The Petition fails to establish obviousness of any of the Ground 2 claims. It relies on *Mata* to purportedly provide (1) “additional evidence of the obviousness of the claims addressed in Ground 1” and (2) “additional limitations of each of dependent claims 10-15, 18, 37-42, and 45...” Pet., 48. For the former, Ground 2 cites no such “additional evidence.” *Id.* For the latter, the Petition fails to establish

motivation to combine the Ground 1 references “in further view of Mata” or establish all claimed limitations. *See* Pet., 46-48.

1. No Motivation to Combine with a Reasonable Expectation of Success

The Petition fails to articulate a “clear and particular” motivation to combine supported by actual evidence.” *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002). Its “rational underpinning” is that

Mata provides additional details about the mechanism by which A2E/lipofuscin is formed (i.e., C20-deprotonation) and also identifies species of lipofuscin-associated ocular diseases that would benefit from retarding lipofuscin formation.

Pet., 53. This (at most) identification of elements fails to show that a POSA “would have selected and combined those prior art elements in the normal course of research and development to yield the claimed invention.” *Unigene Labs., Inc. v. Apotex Inc.*, 655 F.3d 1352, 1360 (Fed. Cir. 2011).

Worse, vitamin A *increasing* per *Ortho* is incompatible with “[p]harmacological inhibition of one or more steps in the A2E synthetic pathway” according to *Mata*. *Intel Corp. v. Koninklijke Philips N.V.*, No. 2022-2034, 2024 WL 725243, at *1 (Fed. Cir. Feb. 22, 2024) (affirming finding that claims were nonobvious where references were “incompatible”); EX2103, 172:23-177:20; EX2104, 14:9-15:2.

2. Dry (non-neovascular) AMD (claim 10, 37), Stargardt’s Disease (claim 11-15, 38-42), and MD + ABCA4 Gene Mutation (claim 18, 45)

The Petition provides no basis to overcome the art and clinical practice *teaching away* from vitamin A supplementation for MD, particularly for Stargardt’s disease or MD characterized by an ABCA4 mutation (as in Stargardt’s disease). Pet., 50-55; §V.A.1; EX1001, 2:13-18; EX2104, 14:4-16:2.

The alleged obviousness further is belied by the untreatability of these blinding diseases that affected millions including children, the many failed treatment attempts, and the further objective indicia associated with the claimed method—including the clinical success of the SAGA and TEASE studies. §V.D.

3. Forms A2E *in vitro* About 7 Times Slower (claim 15, 42)

The Petition fails here for the same reasons as above. §§V.B.3.c, V.E.4.

G. Additional Deficiencies of Ground 3 (Ground 1 and 2 in view of *Widder*): Claims 16-17, 24, 27, 43-44, 51, and 54

Ground 3 piles on, “incorporate[ing] Grounds 1 (Section VI above) and 2 (Section VII above) as a whole but adds the teachings of *Widder* (EX1009).” Pet., 55. As with Ground 2, the Petition (1) does not argue that *Widder* overcomes any of the deficiencies of Grounds 1-2 addressed above and (2) does not provide a rationale to combine its incompatible references. *See* Pet., 56.

1. No Motivation to Combine with a Reasonable Expectation of Success

The Petition fails to articulate a “clear and particular” motivation to combine supported by actual evidence.” *Teleflex, Inc. v. Ficosa North America Corp.*, 299 F.3d 1313, 1334 (Fed. Cir. 2002). Dr. Guengerich’s admission that *Ortho* and *Widder* are “almost diametrically opposed to each other” precludes any such basis to combine. EX2103, 172:23-177:20.

2. Vitelliform or Best Disease, Sorsby’s Fundus Dystrophy, Retinitis Pigmentosa, and Malattia Leventinese (claim 16 (+17), 43 (+44))

Petitioner relies on retinitis pigmentosa (“RP”) to alleged obviousness. Pet., 56-57. But *Widder* “validate[s] a therapeutic approach” based on *lowering* serum retinol and “demonstrate[s] the vitamin-A dependent nature of A2E biosynthesis.” EX1009, 52. This is inconsistent with any motivation or reasonable expectation of success for doing the opposite and administering supplemental vitamin A to RP patients. §V.A; EX2110, 5; EX2158, 8.

3. Phosphatidylglycerol (Claims 24, 51)

The Petition cites *Widder* for disclosing a “pharmaceutical composition comprises cardiolipin and phosphatidylglycerol” with no mention of its rationale for combining with *Ortho* beyond a misplaced argument about “the pharmaceutical compositions of claim 1” and the irrelevant statement that “Ortho Pharma discloses

that vitamin A also can be formulated in various excipients, including aqueous.”

Pet., 60-62.

4. Directly to the Eye (Claims 27, 54)

According to the Petition, *Widder* evidences that “local administration directly to the eye was a desirable route of administration for an active ingredient being administered for the purpose of acting in the eye.” Pet., 63. But *Widder* relies on “*systemic* effects of HPR (e.g., decreased serum retinol levels)” not attributed to ocular administration. EX1009, 16. Moreover, inconsistent with being a nutritional supplement per *Ortho*, the art taught that symptoms of vitamin A deficiency in the retina “would not yield to topical treatment.” EX1028, 1. The Petition fails to provide any reason why C₂₀-deuterated vitamin A administered directly would “function normally in the visual cycle” (Pet., 63-63), given that the transport of vitamin A to the retina occurs through the bloodstream. EX1028, 1.

VI. PETITIONER CONCEALED ITS REAL PARTIES IN INTEREST

The Petition concealed the involvement of related and commonly represented Lin BioScience and Belite Bio and thus failed to “identif[y] all real parties in interest.” 35 U.S.C. §312(a)(2); Paper 11, 5 (failing to provide basis for undenied concealment); EX2027, 4; EX2028, 2-3; EX2029, 4; EX2030, 9; EX2031, 2, 19; EX2032, 6; EX2034, 1; EX2035, 1; EX2039, 1; EX2190 (collectively showing that Belite Bio and its parent Lin BioScience have

overlapping management and control with Petitioner and a vested interest in the outcome of this Petition; commonly represented by Petitioner's counsel). The Petition thus violated non-discretionary statutory requirements that the PTAB lacks authority to waive.

Respectfully submitted,

Dated: September 23, 2024

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. § 42.24(d), I, Mark J. Feldstein, certify that **PATENT OWNER'S RESPONSE** contains 13,090 words, excluding those portions identified in 37 C.F.R. § 42.24(a), as measured by the word-processing system used to prepare this paper.

Dated: September 23, 2024

/Mark J. Feldstein/

Mark J. Feldstein

Reg. No. 46,693

CERTIFICATE OF SERVICE

The undersigned certifies that a copy of the foregoing **Patent Owner's Response** was served electronically via email on September 23, 2024, in its entirety on the following:

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Petitioner has consented to service by electronic mail.

Dated: September 23, 2024

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