

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 IPR2024-00313
Patent RE47,045 E

Before SUSAN L.C. MITCHELL, ZHENYU YANG, and TAWEN
CHANG, *Administrative Patent Judges*.

CHANG, *Administrative Patent Judge*.

JUDGMENT
Final Written Decision
Determining No Challenged Claims Unpatentable
35 U.S.C. § 318(a)
Dismissing Petitioner's Motion to Exclude Evidence as Moot
37 C.F.R. § 42.64

I. INTRODUCTION

This is a Final Written Decision in an *inter partes* review challenging the patentability of claims 1–54 of U.S. Patent No. RE47,045 E (Ex. 1001, “the ’045 patent”). We have jurisdiction under 35 U.S.C. § 6.

Petitioner has the burden of proving unpatentability of the challenged claims by a preponderance of the evidence. 35 U.S.C. § 316(e). Having reviewed the parties’ arguments and cited evidence, for the reasons discussed below, we find Petitioner has not demonstrated by a preponderance of the evidence that claims 1–54 are unpatentable. Additionally, for the reasons discussed below, we dismiss Petitioner’s Motion to Exclude as moot.

A. *Procedural History*

Petitioner Gene Company Pty Ltd filed a Petition requesting *inter partes* review of claims 1–54 of the ’045 patent. Paper 2 (“Pet.”). Patent Owner, the Trustees of Columbia University in the City of New York, timely filed a Preliminary Response. Paper 9 (“Prelim. Resp.”). The parties further submitted an authorized Reply and Sur-Reply to the Preliminary Response. Paper 11; Paper 12; Ex. 3001. In view of the then-available preliminary record, we instituted an *inter partes* review. Paper 13 (“Inst. Dec.”).

After institution, Patent Owner filed a Response to the Petition. Paper 23 (“PO Resp.”). Petitioner filed a Reply. Paper 32¹ (“Reply”). Patent Owner filed a Sur-reply. Paper 37 (“Sur-reply”).

Petitioner filed a Motion to Exclude certain evidence. Paper 44 (“Mot.”). Patent Owner opposed that motion. Paper 46 (“Opp.”). Petitioner filed a Reply. Paper 48 (“Mot. Reply”).

On March 27, 2025, we held an oral hearing, the transcript of which is of record. Paper 52 (“Tr.”).

B. Real Parties-in-Interest

Petitioner identifies itself as the real party-in-interest. Pet. 19. Patent Owner identifies itself and “Alkeus Pharmaceuticals, Inc., the exclusive licensee of the ’045 patent,” as the real parties-in-interest. Paper 4, 2.

Patent Owner asserts in its Preliminary Response that the Petition should be denied because “it appears to have concealed the involvement of Lin BioScience and Belite Bio” and, thus, “does not meet the requirements of 35 U.S.C. § 312(a).” Prelim. Resp. 73; *see also* Paper 12, 1. Because there was no time bar or estoppel implication with respect to Lin BioScience and Belite Bio, we instituted *inter partes* review without addressing whether these entities should be named as real parties-in-interest, consistent with Board precedent. *SharkNinja Operating LLC v. iRobot Corp.*, IPR2020-00734, Paper 11, 18–20 (PTAB Oct. 6, 2020) (precedential) (“SharkNinja”). Inst. Dec. 3–4. In our Institution Decision, we denied Petitioner’s request

¹ Paper 32 is sealed (i.e., available to the parties and Board only); a redacted version appears as Paper 31.

for authorization to identify Lin BioScience and Belite Bio as “potential” real parties-in-interest, but noted that Petitioner may renew its request “[i]f and when Petitioner determines in good faith that Lin BioScience and Belite Bio, or any other parties, should be identified as real parties-in-interest” under 35 U.S.C. § 312(a)(2). *Id.* Petitioner has not renewed its request.

In its Response after institution, Patent Owner again asserts that “[t]he 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.’” PO Resp. 63 (alternation in original). Patent Owner asserts that “[t]he Petition thus violated non-discretionary statutory requirements that the PTAB lacks authority to waive.” *Id.* at 64; *see also* Sur-reply 28. Petitioner asserts that Patent Owner’s arguments are “baseless.” Reply 28.

Patent Owner does not allege a time bar or estoppel issue in this proceeding based on the alleged status of Lin BioScience and Belite Bio as real parties-in-interest. Accordingly, because whether Lin BioScience and Belite Bio are real parties-in-interest does not impact this proceeding,² we do not make any determinations with respect to this issue.

² For this reason, *Semiconductor Components Industries, LLC, d/b/a Onsemi v. Greenthread, LLC*, IPR2023-01242, Paper 92 (USPTO Director April 24, 2025) (“*Greenthread*”) does not dictate a contrary result. There, unlike in this case, Patent Owner argued that the petitions at issue were untimely under 35 U.S.C. § 315(b) due to a district court complaint served on Petitioner’s alleged privy more than one year before the petitions were filed. *Greenthread*, 2.

C. Related Proceedings

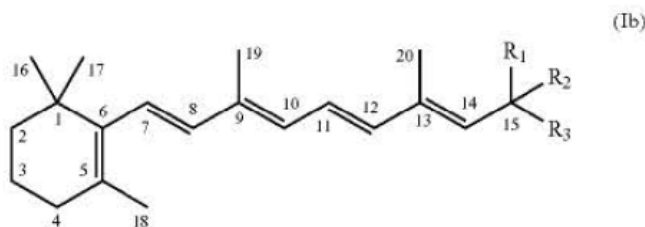
Petitioner states that “[a] petition was filed in IPR2024-00312 against U.S. Patent No. 9,486,432, which is a continuation” of U.S. Patent No. 8,877,809 B2 (the ’809 patent), of which RE47,045 is a reissue. Pet. 19. Patent Owner similarly identifies IPR2023-00312 as a related matter and states that it is “unaware of any other judicial or administrative proceeding involving the ’045 patent.” Paper 4, 2.³

The parties do not identify any other patent or application claiming, or that may claim, the benefit of the priority of the filing date of the ’045 patent or Application Serial No. 15/343,016 (“the ’016 application). Pet. 19–20; Paper 4, 2–3; Paper 6; 0–2; Paper 8, 1–3; Paper 39, 1–2.

D. The ’045 Patent and Relevant Background

1. Vitamin A and Retinoid Compounds

A retinoid is a compound having the following general structure:

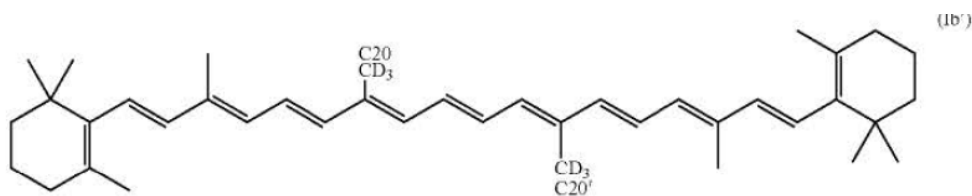


Ex. 1001, 10:40–50. The above figure shows the general chemical structure of a class of compounds called retinoids, comprising three generic

³ The Board entered adverse judgment against Patent Owner because Patent Owner abandoned the contest in IPR2024-00312. *Gene Co. Pty Ltd v. Trustees of Columbia Univ. in the City of New York*, IPR2024-00312, Paper 16 (PTAB Jan. 28, 2025).

placeholder groups R_1 , R_2 , and R_3 attached to the carbon atom labeled C_{15} . When R_1 and R_2 are both hydrogen (H) and R_3 is a hydroxide (OH), the compound is retinol. *Id.* at 10:55. When R_1 and R_2 are both H and R_3 is an ester group (OCOR), the compound is a retinol ester. *Id.* at 10:59–60. When R_1 is H, R_2 is nothing, and R_3 is a carbonyl group ($=O$), the compound is retinal, sometimes referred to as retinaldehyde. Ex. 1002 ¶ 59; Ex. 2052 ¶ 62 (Fig. 4); Ex. 1010, Fig. 5 (referring to compound with this structure as retinaldehyde or RAL). Vitamin A refers to a group of retinoid compounds, including retinol, retinal, retinoic acid, and retinol (or retinyl) ester. Ex. 1002 ¶¶ 59, 64; *see also* Ex. 2052 ¶ 60 (referring to all-*trans*-retinol as vitamin A), Ex. 1069 ¶ 20 (“All-*trans*-retinol is vitamin A”), Ex. 2104, 34:11–18 (stating that “vitamin A is an inclusive term that includes retinol, retinal, retinoic acid, retinyl acetate,” among others).

Carotenoids are “naturally-occurring yellow to red pigments” that may be precursors of vitamin A. Ex. 1001, 9:29–33, 14:44–47. An example of a provitamin A carotenoid is β -carotene, the structure of which is reproduced below:

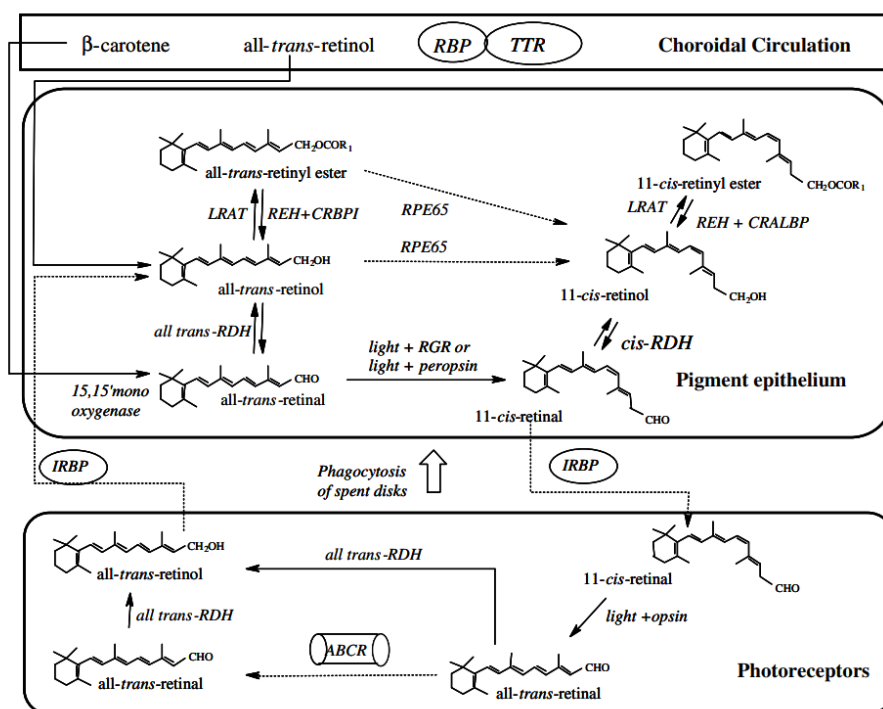


Ex. 1001, 11:1–9. The figure above shows the chemical structure of β -carotene, having the chemical formula $C_{40}H_{56}$.⁴

⁴ The structure reproduced above has been deuterated at two locations (C20

2. Visual Cycle

Phototransduction in the eye, which converts light into signals processed by the brain, “relies on light-induced isomerization of the chromophore, 11-*cis*-retinal (or derivative), to all-*trans*-isomer,” and “[t]he regeneration of pre-illumination conditions requires reformation of 11-*cis*-retinoids.” Ex. 1050, 2959 (left column); Ex. 2192 ¶ 56. This mechanism of chromophore regeneration is “termed the ‘visual cycle’ or the retinoid cycle.” *Id.* The figure below, reproduced from Kuksa⁵ illustrates the steps in the visual cycle:

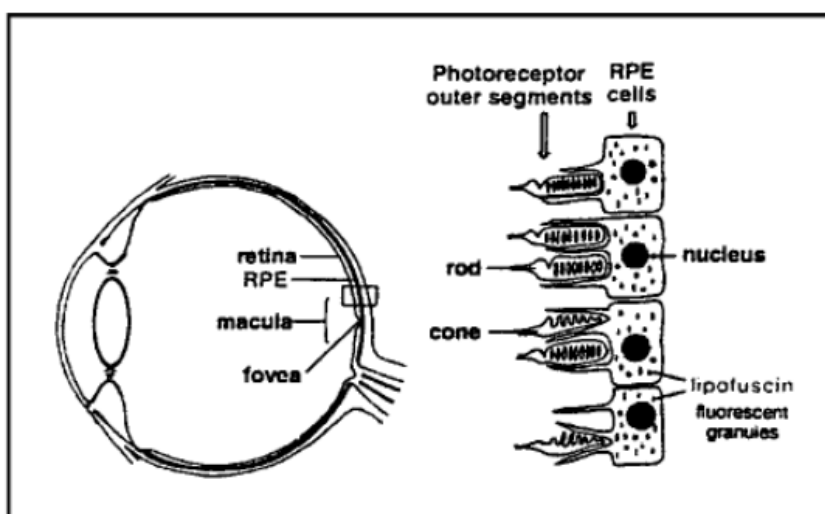


and C20'). Ex. 1001, 10:66–11:9. We discuss deuteration below. *See infra* Section I.D.4.

⁵ Kuksa et al., *Retinoid Cycle in the Vertebrate Retina: Experimental*

The above figure is a “[s]chematic representation of the visual cycle in rod-dominant animals, based on genetic and biochemical evidence.” Ex. 1050, 2960, Fig. 1.⁶ As shown in the figure, the visual cycle takes place in both the photoreceptors and the pigment epithelium. *Id.*

The relative locations of the photoreceptors and retina pigment epithelium (RPE) in the eye is illustrated in the figure below:



Ex. 1034, 343, Fig. 1. The above figure is a diagram of the eye, which shows the location of the retina, comprising photoreceptors, retinal pigment

Approaches and Mechanisms of Isomerization, 43 VISION RES. 2959 (2003) (Ex. 1050, “Kuksa”).

⁶ The abbreviations used in the figure include: “ABCR, a photoreceptor-specific, ATP-binding cassette transporter; CRALBP, cellular retinaldehyde-binding protein; CRBP1, cellular retinol-binding protein 1; IRBP, interphotoreceptor retinoid-binding protein; LRAT, lecithin:retinol acyltransferase; RGR, RPE G protein-coupled receptor; RPE65, retinal pigment epithelial (cells) 65 kDa protein; RBP, retinol-binding protein; RDH, retinol dehydrogenase; REH, retinyl ester hydrolase, TTR, transthyretin.” Ex. 1050, 2960, Fig. 1 (caption).

epithelium (RPE), and macula. The call-out depicts a portion of the eye comprising photoreceptor (rod and cone) outer segments and retinal pigment epithelium (RPE) cells.

3. Macular Dystrophies

“The macula is located at the back of the eye in the center of the retina. When the millions of cells in this light-sensitive, multilayer tissue deteriorate, central vision is lost.” Ex. 1001, 1:43–45. “This ‘macular degeneration’ principally affects the elderly,” but also may be found in younger populations in individuals with certain genetic disorders, such as Stargardt disease. *Id.* at 1:47–55.

Macular dystrophies are marked by the accumulation, in the retinal pigment epithelium, of lipofuscin, which are fluorescent deposits that contain the compounds N-retinylidene-N-retinylethanolamine (A2E) and all-trans-retinal dimer (ATR dimer), among others. Ex. 1001, 1:65–2:3. The ’045 patent states that A2E and ATR dimer are derived from reactions of all-trans-retinal — discussed above as part of the visual cycle — and “increasing the amount of all-trans-retinal in outer segments [of photoreceptors], such as occurs with the mutations in *abcr*^{−/−} (responsible for recessive Stargardt disease), leads to the rapid accumulation of lipofuscin pigments.”⁷ *Id.* at 2:1–5, 2:13–17.

⁷ The ABCR (or the ABCA4) gene encodes “a photoreceptor-specific adenosine triphosphate (ATP)-binding cassette transporter,” which is needed in the visual cycle to “properly shuttle vitamin A (in the form of retinal) in the eye.” Ex. 1001, 2:26–30; Ex. 1050, 2960, Fig. 1. “ABCR^{−/−} mice

The '045 patent states that “A2E and the ATR-dimer are believed to be formed in vivo by a multi-step reaction sequence involving two molecules of all-trans-retinal,” as shown in its Figure 2 reproduced below. Ex. 1001, 7:60–63.

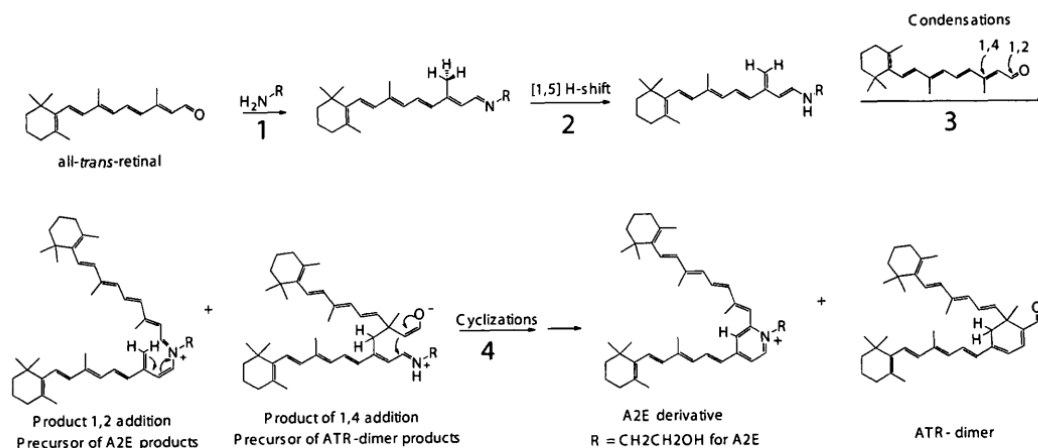


FIG 2.

The figure above sets forth “a reaction scheme showing the biosynthesis of A2E and ATR-dimer from all-trans-retinal and a biological amine.” *Id.* at 6:21–23. The '045 patent states, with respect to A2E and ATR-dimer, that “[t]hese toxic retinal dimers have been shown to cause RPE cell death, which is thought to lead to photoreceptor cell degeneration and vision loss.” *Id.* at 2:5–8.

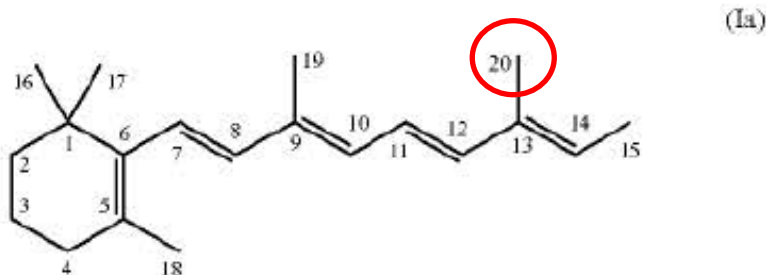
accumulate large lipofuscin deposits in RPE cells of their eyes . . . and eventually experience delayed dark adaption.” Ex. 1001, 2:32–35. Such mice have been “used to test approaches to limit RPE lipofuscin formation.” *Id.* at 2:25–26.

4. Claimed Invention

The '045 patent states that slowing the visual cycle, for instance by limiting dietary intake of vitamin A (retinol) and thereby retarding its delivery to RPE, “have been shown to impede or abolish RPE lipofuscin formation in animal models.” Ex. 1001, 2:8–17. The '045 patent states, however, that “[t]here are . . . disadvantages to slowing the visual cycle as a means to impede lipofuscin in order to prevent, e.g., macular degeneration.” *Id.* at 3:34–36. These disadvantages include “delayed dark adaptation and poor vision in dim light or at night”; “photoreceptor cell death and loss of vision” in the case of “long-term slowing of the visual cycle”; toxicities and potentially “significant adverse side effects” where vitamin A analogs are used to slow the visual cycle; and the likely need for “relatively large doses” of candidate drugs and concomitant increase in side effects. *Id.* at 3:38–5:18.

The '045 patent discloses using C₂₀-D₁₋₃-retinoid to retard formation of a lipofuscin pigment in the retina and to treat or ameliorate ophthalmologic disorders such as macular degeneration. *See, e.g.*, Ex. 1001, 8:29–32, 8:41–52, 9:3–13. In a C₂₀-D₁₋₃-retinoid, one, two, or three of the hydrogens attached to C₂₀ are replaced with deuterium, an isotope of hydrogen. *Id.* at 8:29–34. Formula Ia, reproduced below from the '045 patent, sets forth the scheme for numbering carbons in a retinoid for

purposes of the invention. For clarity, we have circled C₂₀ in red in the formula.



The above figure depicts a chemical formula setting forth the number scheme for carbons in retinoids, with C₂₀ circled in red. *Id.* at 10:17–34 (annotation in red added).

The '045 patent states that,

[w]hen C₂₀ hydrogens are replaced by deuteriums, A2E formation is about seven times slower (FIG. 3) and ATR-dimer formation is about 15 times slower (FIG. 4). This kinetic isotope effect will slow A2E and ATR-dimer formation in vivo. Deuterated vitamin A is widely used in humans and shows no toxicity (45, 46). Thus, a treatment using a C₂₀-D₁₋₃-retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects.

Ex. 1001, 8:31–40.⁸

⁸ “Kinetic isotope effect” (KIE) generically refers to “the difference in the rate of reaction caused by substituting an atom in a molecule with one of its heavier isotopes, e.g., replacing hydrogen with deuterium.” Ex. 2052 ¶ 130; *see also* Ex. 1002 ¶ 108.

E. The Challenged Claims

Petitioner challenges all fifty-four claims of the '045 patent. Claims 1, 28, and 29 are independent. Independent claim 28, reproduced below, is illustrative:

28. A method of treating a macular degeneration, comprising administering an effective amount of a substituted C₂₀-D₁₋₃-retinoid to a patient in need thereof, wherein the C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₁₋₃-retinol, C₂₀-D₁₋₃-retinol ester, C₂₀-D₁₋₃-retinal, and C₂₀-D₁₋₃-pro-vitamin A carotenoids.

Claim 1 recites a method of retarding the accumulation of a lipofuscin pigment in a retina, comprising administering an effective amount of a pharmaceutical composition to a patient in need thereof, wherein the pharmaceutical composition comprises a substituted C₂₀-D₁₋₃-retinoid as recited in claim 28 and a pharmaceutically acceptable carrier. Claim 29 recites a method of treating a macular degeneration, comprising administering an effective amount of the pharmaceutical composition recited in claim 1 to a patient in need thereof.

Among the challenged dependent claims, claims 2–27 and 30–54 depend directly or indirectly from claims 1 and 29, respectively.

Claims 4, 5, 10, 11, 16, 18, 32, 37, 38, 43, and 45, and their dependent claims, further limit the patient to those in need of treatment for particular condition or conditions: “a macular degeneration” (claim 4), “age-related macular degeneration” (claims 5, 32), “dry (non-neovascular) age-related macular degeneration” (claims 10, 37), “Stargardt disease” (claims 11, 38), “a macular degeneration selected from the group consisting of Vitelliform or

Best disease, Sorsby's fundus dystrophy, retinitis pigmentosa, and Malattia Leventinese" (claims 16, 17, 43, 44), or "macular degeneration characterized by one or more mutation(s) in the ABCA4 gene" (claims 18, 45).

Claims 2, 6–8, 12–14, 17, 30, 33–35, 39–41, and 44, and their dependent claims, are further limited to particular recited C₂₀-D₁₋₃-retinoid(s): C₂₀-D₃-retinoid (claims 2, 30); C₂₀-D₁₋₃-retinol or C₂₀-D₁₋₃-retinol ester (claims 6, 12, 33, 39); C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal, or a C₂₀-D₃-pro-vitamin A carotenoid (claims 7, 13, 34, 40); or C₂₀-D₃-retinol acetate (claims 8, 14, 17, 35, 41, 44).

Finally, claims 20–25 and 47–52 further comprise administering additional recited active(s); claims 3 and 31 further recite that "the pharmaceutical composition is suitable for use as a nutraceutical composition"; claims 9, 15, 26, 36, 42, and 53 further recite that "the C₂₀-D₁₋₃-retinoid forms A2E about 7 times slower than non-deuterium enriched retinoid"; and claims 19, 27, 46, and 54 further recite limitations regarding dosage amounts and route of administration.

F. The Asserted Grounds of Unpatentability

We instituted trial based on the following grounds of unpatentability:

Ground	Claim(s) Challenged	35 U.S.C § ⁹	Reference(s)/Basis
1	1–9, 19–23, 25, 26, 28–36, 46–50, 52, 53	103(a)	Ortho Pharma, ¹⁰ Bergen ¹¹
2	10–15, 18, 37–42, 45	103(a)	Ortho Pharma, Bergen, Mata ¹²
3	16, 17, 24, 27, 43, 44, 51, 54	103(a)	Ortho Pharma, Bergen, Mata, Widder ¹³

Inst. Dec. 2, 20, 61; Pet. 20–21.

Petitioner supports its contentions with two declarations from F. Peter Guengerich, Ph.D. (Exs. 1002, 1080) and a declaration from Andrew

⁹ The Leahy-Smith America Invents Act (“AIA”), Pub. L. No. 112-29, 125 Stat. 284, 287–88 (2011), amended 35 U.S.C. § 103, effective March 16, 2013. Because the application from which the ’045 patent issued claims an effective filing date prior to March 16, 2013, which Petitioner does not contest, we apply the pre-AIA version of 103. *See* Ex. 1001, code (60) (listing provisional patent application filed on September 12, 2007); *see also* Pet. 4; Ex. 1002 ¶ 15; Ex. 1004 ¶ 13.

¹⁰ DE 20 2006 014 588 U1, filed September 20, 2006, and published January 18, 2007 (English translation) (Ex. 1008, “Ortho Pharma”).

¹¹ Bergen et al., *Synthesis of Tri-, Tetra-, and Penta-deuterated Forms of Vitamin A*, 25 J. LABELLED COMPOUNDS AND RADIOPHARMS. 11 (1988) (Ex. 1006, “Bergen”). We note that parties refer to Ex. 1006 as “Olson 1988.” We refer to Ex. 1006 as “Bergen,” according to the Board’s convention of using the first author’s last name to denote a reference.

¹² Mata et al., *Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration*, 97 PNAS 7154 (2000) (Ex. 1010, “Mata”).

¹³ Widder et al., WO 2006/007314 A1, published Jan. 19, 2006 (Ex. 1009, “Widder”).

Calman, M.D., Ph.D. (Ex. 1004), among other evidence. Patent Owner supports its contentions with declarations from Glenn Prestwich, Ph.D. (Ex. 2052) and Lucian V. Del Priore, M.D., Ph.D. (Ex. 2192), among other evidence. Patent Owner also relies on a declaration from Leonide Saad, Ph.D. (Ex. 2191) in its Response for its contentions regarding objective indicia of non-obviousness.

II. ANALYSIS

A. *Level of Ordinary Skill in the Art*

1. Defining the Level of Ordinary Skill in the Art

We consider the grounds of unpatentability in view of the understanding of a person of ordinary skill in the art as of the time of the invention of the challenged claims. *See, e.g., Graham v. John Deere Co.*, 383 U.S. 1, 17–18 (1966).

The parties’ competing definitions for the level of skill of a person of ordinary skill in the art (sometimes referred to herein as “POSA” or “ordinarily skilled artisan”) are set forth below:

Petitioner	Patent Owner
A POSA . . . would have had an advanced degree (e.g., Ph.D., M.D., M.S., or equivalent), in chemistry, biochemistry, pharmaceutical science, medicine, or a related field. This individual may have worked in consultation with a team including, e.g., a practicing physician who diagnoses and treats macular degeneration. Moreover, skilled	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

Petitioner	Patent Owner
artisans would have had practical knowledge about biological studies, pharmaceutical formulation, and the deuterium isotope effect, including the patents and publications discussed herein. Pet. 7.	(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. PO Resp. 7–8.

Patent Owner asserts that Petitioner’s definition of level of ordinary skill in the art is erroneous because it (1) “requires *no* specialized skill beyond a general ophthalmologist,” (2) “improperly ‘used the invention to define the problem that the invention solves’” by specifying that a POSA would have “had practical knowledge about . . . the deuterium isotope effect,” and (3) “improperly relies on a ‘team’ proposal to combine separate opinions as to what would have been obvious from ‘the perspective of a chemist’ and . . . the ‘perspective of a clinician.’” PO Resp. 8–9.

Petitioner asserts that Patent Owner “redefines the POSA to ignore KIE” (kinetic isotope effect) and that the definition “disregards” the fact that “practical knowledge about deuterium KIE was in the POSA’s toolkit.” Reply 14 (citing, *e.g.*, Ex. 1070, 37:3–10; Ex. 2052 ¶¶ 129–130, 139, 152).

As an initial matter, we do not find there to be a substantial difference between Petitioner’s proposal that an ordinarily skilled artisan “may have worked in consultation with a team” including individuals with additional or different qualifications and Patent Owner’s proposal that an ordinarily skilled artisan “may consult with others” having additional or different qualifications. Describing a person of ordinary skill as part of a “team” is not per se impermissible, so long as testimony relating to issues of obviousness is offered from the vantage point of the ordinarily skilled artisan. *Indivior Inc. v. Dr. Reddy’s Labs., S.A.*, 930 F.3d 1325, 1343 (Fed. Cir. 2019) (finding no clear error in the district court’s determination that “a person of ordinary skill would principally have a background in pharmaceutical science or chemistry but ‘would be on a team with an engineer or scientist with one to three years of relevant experience’”).

Instead, the primary differences between the parties’ proposals are (1) whether the level of skill of an ordinarily skilled artisan should be explicitly defined to include “practical knowledge about . . . deuterium isotope effect, including the patents and publications discussed [in the Petition],” and (2) whether such an artisan must have experience researching “biosynthesis and structure of naturally occurring terpenoids . . . and/or methods to slow lipofuscin formation or accumulation to treat an ophthalmologic disorder, such as AMD or Stargardt.” *Compare* Pet. 7, with PO Resp. 7–8.

As to the first issue, we agree with Patent Owner that defining the level of skill in view of the solution described in the patent risks improper hindsight. *Okajima v. Bourdeau*, 261 F.3d 1350, 1355 (Fed. Cir. 2001)

("[T]he level of skill in the art is a . . . lens through which . . . the Board views the prior art and the claimed invention," which "prevents . . . factfinders from using their own insight or . . . hindsight[] to gauge obviousness."). We therefore do not include "practical knowledge about . . . the deuterium isotope effect, including the patents and publications discussed [in the Petition]," as part of our definition of a person of ordinary skill in the art.

In considering the second issue, we take into account factors pertinent to a determination of the level of ordinary skill in the art, which include: "(1) the educational level of the inventor; (2) type of problems encountered in the art; (3) prior art solutions to those problems; (4) rapidity with which innovations are made; (5) sophistication of the technology; and (6) educational level of workers active in the field. *Env't Designs, Ltd. v. Union Oil Co.*, 713 F.2d 693, 696 (Fed. Cir. 1983). "Not all such factors may be present in every case, and one or more of these or other factors may predominate in a particular case." *Id.* at 696–697. Moreover, "[t]hese factors are not exhaustive but are merely a guide." *Daiichi Sankyo Co. v. Apotex, Inc.*, 501 F.3d 1254, 1256 (Fed. Cir. 2007). Finally, the prior art itself may reflect an appropriate skill level. *Okajima*, 261 F.3d at 1355.

Having considered the factors above, we agree with Patent Owner that to be a POSA in this case would require more than an M.D., as is permitted by Petitioner's definition so long as that M.D. also has "practical knowledge about biological studies, pharmaceutical formulation, . . . the deuterium isotope effect, [and] the patents and publications discussed [in the Petition]." However, based on our review of the '045 patent and the prior art of record,

we are not persuaded that an ordinarily skilled artisan must have “research experience in biosynthesis and structure” of the specific compounds (naturally-occurring terpenoids) and/or the particular method of treating an ophthalmologic disorder (“slowing lipofuscin formation or accumulation”) at issue in the ’045 patent.

Accordingly, on the full trial record, we adopt Patent Owner’s definition of the person of skill in the art with modifications as follows:

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 or working with naturally-occurring terpenoids (e.g., retinoids and bis-retinoids such as lipofuscin pigments, carotenoids, steroids) and/or methods to treat an ophthalmologic disorder. The POSA may consult with others, such as a biochemist, formulation scientist, or practicing a physician who diagnoses and treats macular degeneration.

Based on our review of the ’045 patent and the prior art of record, we determine that the above definition comports with the skill level reflected in the prior art of record and the disclosure of the ’045 patent. We note, however, that the outcome of this Decision would be the same under either party’s proposed definition.

2. Whether Petitioner’s Experts Qualify as Persons of Ordinary Skill in the Art

a) Dr. Guengerich

Patent Owner argues that Dr. Guengerich “lacks the minimum experience to qualify as a POSA or provide expert testimony in this

proceeding” because (1) “[h]is work focuses nearly exclusively on enzymatic reactions”; (2) “[h]e lacks experience with lipofuscin formation”; and (3) “[h]e . . . lacks credibility” because his testimony in this case is contradicted by his prior statements. PO Resp. 12 (citing Ex. 2083, 1; Ex. 2056, 1–2; Ex. Ex. 2057, 2); *see also* Sur-reply 27–28 (arguing that Dr. Guengerich “lacks any knowledge or experience in treating any ophthalmologic disease,” “undermined his own credibility,” and “did not address Dr. del Priore’s declaration or the majority of the references cited therein”).

Based on Dr. Guengerich’s qualifications as set forth in his declaration, CV, and deposition testimony, we are persuaded that Dr. Guengerich qualifies as at least a person of ordinary skill in the art under the definition we adopted above. Ex. 1002 ¶¶ 1–12; Ex. 1003; Ex. 1080 ¶ 15.

First, even if Dr. Guengerich’s work focuses on enzymatic reactions, he has had experience working with retinoids. Ex. 1002 ¶ 12; Ex. 1080 ¶ 15. Although this work with retinoids appears to have started after the effective filing date, a person of ordinary skill in the art need not have been one of ordinary skill at the time of the invention. *Osseo Imaging, LLC v. Planmeca USA Inc.*, 116 F.4th 1335, 1341 (Fed. Cir. 2024) (declining to impose a requirement that “an expert must be a person of ordinary skill in the art *at the time of the invention* to offer expert testimony from the vantage point of a skilled artisan” and holding that “an expert can acquire the necessary skill level later and develop an understanding of what a person of ordinary skill knew at the time of the invention”).

As to Patent Owner's argument that Dr. Guengerich lacks experience with lipofuscin formation or knowledge or experience in treating ophthalmic diseases, this is not a requirement in the level of ordinary skill in the art we have adopted for this case. Indeed, experience with lipofuscin formation or knowledge or experience treating ophthalmic diseases is not a requirement in Patent Owner's own proposal, which only requires a person of ordinary skill to have 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." PO Resp. 7–8 (emphasis added).

Finally, even assuming Dr. Guengerich's testimony in this case is contradicted by his prior statements, the alleged contradictions do not disqualify him from meeting the level of ordinary skill in the art, and the Board is well-positioned to determine and assign appropriate weight to the presented evidence, including based on credibility. *See, e.g., Corning Inc. v. DSM IP Assets B.V.*, IPR2013-00053, Paper 66 at 19 (PTAB May 1, 2014) ("[T]he Board, sitting as a non-jury tribunal, is well-positioned to determine and assign appropriate weight to the evidence presented in this trial.").

b) Dr. Calman

Patent Owner asserts that Dr. Calman "lacks the minimum experience to qualify as a POSA or provide expert testimony in this proceeding" because (1) "he is a general practice ophthalmologist and professional witness"; (2) he 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 a AMD or Stargardt's disease"; (3) "[h]e does not attempt to treat Stargardt's patients, instead referring them to an expert"; (4) "his clinical research experience is limited to diabetes, glaucoma, and monitoring ocular side effects." PO Resp. 10–11. Patent Owner argues that Dr. Calman "does not understand the art on which he relies" and instead "defer[s] to Dr. Guengerich," and "further undermines his own credibility with evasive and nonresponsive testimony." *Id.* at 11.

We are persuaded that Dr. Calman qualifies as a person of ordinary skill in the art under the definition we have adopted for this case.

In particular, Dr. Calman testified that, in addition to being a doctor of medicine, he has "a master's in molecular biophysics and chemistry, a Ph.D. in microbiology and immunology, which included coursework in biochemistry, and . . . use[s] biochemical techniques in [his] research in the lab." Ex. 1005; Ex. 2104, 53:12–16. He also has significant experience diagnosing and treating patients with macular disease, as well as experience researching methods to treat ophthalmological disorders. Ex. 2104, 11:17–18; Ex. 1004 ¶¶ 8, 9; Ex. 1005.

Neither Dr. Calman's prior work as an expert witness nor Patent Owner's characterization of his testimony as "evasive and nonresponsive" disqualifies him from meeting the level of ordinary skill in the art. As noted above in our discussion of Dr. Guengerich's qualifications, the Board is well-positioned to determine and assign appropriate weight to the presented

evidence, including based on credibility. *See, e.g., Corning Inc.*, IPR2013-00053, Paper 66 at 19.

Finally, Dr. Calman’s reliance on Dr. Guengerich’s testimony for certain topics is also not improper: Our definition of the level of ordinary skill—as well as definitions proposed by both parties—permits a POSA to consult with others having additional specialized knowledge.

Accordingly, based on their statements of qualifications and curricula vitae, and in view of the discussion above regarding the qualifications of Drs. Guengerich and Calman, we find that Petitioner’s declarants, Drs. Guengerich and Calman, and Patent Owner’s declarants, Drs. Prestwich and Del Priore, are qualified to provide technical opinions from the perspective of a person of ordinary skill in the art in this proceeding. Ex. 1002 (Guengerich Decl.) ¶¶ 2–12; Ex. 1003 (Dr. Guengerich’s curriculum vitae); Ex. 1004 (Calman Decl.) ¶¶ 2–10; Ex. 1005 (Dr. Calman’s curriculum vitae); Ex. 2052 (Prestwich Decl.) ¶¶ 3–22; Ex. 2053 (Dr. Prestwich’s curriculum vitae); Ex. 2192 (Del Priore Decl.) ¶¶ 5–18; Ex. 2193 (Dr. Del Priore’s ’s curriculum vitae).¹⁴

B. Claim Construction

We construe claims “using the same claim construction standard that would be used to construe the claim in a civil action under 35 U.S.C. [§] 282(b).” 37 C.F.R. § 42.100 (2023). Therefore, we construe the challenged claims under the framework set forth in *Phillips v. AWH Corp.*,

¹⁴ Petitioner moved to exclude certain portions of Dr. Del Priore’s testimony during trial. Mot. 7. As noted, we dismiss that motion as moot.

415 F.3d 1303, 1312–19 (Fed. Cir. 2005) (en banc). Under this framework, claim terms are given their ordinary and customary meaning, as would be understood by a person of ordinary skill in the art, at the time of the invention, in light of the language of the claims, the specification, and the prosecution history of record. *Id.*

Petitioner “submits that no construction should be necessary,” although it notes that “[t]he specification of the ’045 patent confirms that the claim term ‘pharmaceutically acceptable carrier’ encompasses a wide variety of conventional carriers, including water, saline solution, corn oil, and starch.” Pet. 21 (citing Ex. 1002 ¶ 185; Ex. 1004 ¶ 105). In addition, Petitioner states in its analysis of claim 28 that “[t]he preamble is not limiting and is entitled to no patentable weight.” *Id.* at 23. Finally, during the hearing, Petitioner emphasized that the term “patient,” which is present in all of the independent claims, includes non-human animals such as mice. Tr. 26:22–25 (Petitioner arguing that the “reasonable expectation” threshold requires only to “give a vitamin supplement to a mouse”).

Patent Owner does not take issue with Petitioner’s assertion regarding the scope of “pharmaceutically acceptable carrier.” However, Patent Owner asserts that the preambles of all of the independent claims “should all be construed as limiting as they ‘giv[e] life and meaning to the method step of each claim’” PO Resp. 12 (quoting *Eli Lilly & Co. v. Teva Pharms. Int’l GmbH*, 8 F.4th 1331, 1343 (Fed. Cir. 2021)). Patent Owner asserts Petitioner has not previously argued that patient should be construed to include mice and that, in any event, the construction of “patient” is not relevant to Petitioner’s obviousness grounds. Tr. 52:22–53:11.

In our Institution Decision, we preliminarily construed the preamble of claim 28 as limiting. Inst. Dec. 30–31. Petitioner did not take issue with our construction, or dispute Patent Owner’s construction of the preambles of claims 1 and 29 as also limiting. After consideration of the full trial record, we maintain our construction of the preamble of claim 28 as limiting for the reasons set forth in our Institution Decision. For similar reasons and the reasons set forth in Patent Owner’s Response, we further construe the preambles of claims 1 and 29 as limiting. *See* PO Resp. 12–14. We further determine that we do not need to construe any other claim term in order to resolve the controversy between the parties. *See Realtime Data, LLC v. Iancu*, 912 F.3d 1368, 1375 (Fed. Cir. 2019) (“The Board is required to construe ‘only those terms . . . that are in controversy, and only to the extent necessary to resolve the controversy.’”) (quoting *Vivid Techs., Inc. v. Am. Sci. & Eng’g, Inc.*, 200 F.3d 795, 803 (Fed. Cir. 1999)).

C. Overview of Asserted References

1. Overview of Ortho Pharma (Exhibit 1008)

Ortho Pharma is a certified translation of a German Patent Publication for a “[c]arotenoid-containing product.” Ex. 1008, code (54); Ex. 1023. Ortho Pharma teaches that age-related eye disease, such as age-related macular degeneration, “can be aggravated . . . by an incorrect diet or an inadequate supply of the necessary vitamins and nutrients.” Ex. 1008 ¶¶ 2–3.

Ortho Pharma teaches “a carotenoid-containing product that is particularly suitable for balanced nutritive supplementation of the diet in age-related eye diseases such as age-related macular degeneration or senile

cataract.” Ex. 1008 ¶ 1; *see also id.* ¶¶ 11, 25 (teaching that “[p]roviding the eye with carotenoids may particularly help to provide nutritive support for the eye in age-related macular degeneration or senile cataracts”), 52 (stating “[t]he carotenoid-containing product can be used for dietary treatment of age-related eye diseases” such as age-related macular degeneration or senile cataract), 54.

Ortho Pharma teaches embodiments comprising particular amounts of vitamins A, B₁, B₂, B₆, B₁₂, C, D₃, and E; nicotinamide; folic acid; biotin; pantothenic acid; trace elements including zinc, selenium, and chromium; sulfur-containing amino acids including L-cystine, N-acetylcysteine, and taurine; omega-3 fatty acids; and secondary plant compounds including carotenoids and flavonoids. Ex. 1008 ¶ 19; *see also id.* ¶¶ 8, 9, 24, 36, 41–44, 46, 47, 49.

2. Overview of Bergen (Exhibit 1006)

Bergen teaches methods of synthesis for “20, 20, 20-trideutero, 14, 20, 20, 20-tetradutero, 12, 14, 20, 20, 20-pentadeutero . . . analogs of retinoic acid ethyl ester and retinyl acetate.” Ex. 1006, 11, Summary. Bergen teaches that such “nonradioactive deuterated or ¹³C labeled compounds of high purity are desired” for studying the metabolism of vitamin A in humans. *Id.* at 11.

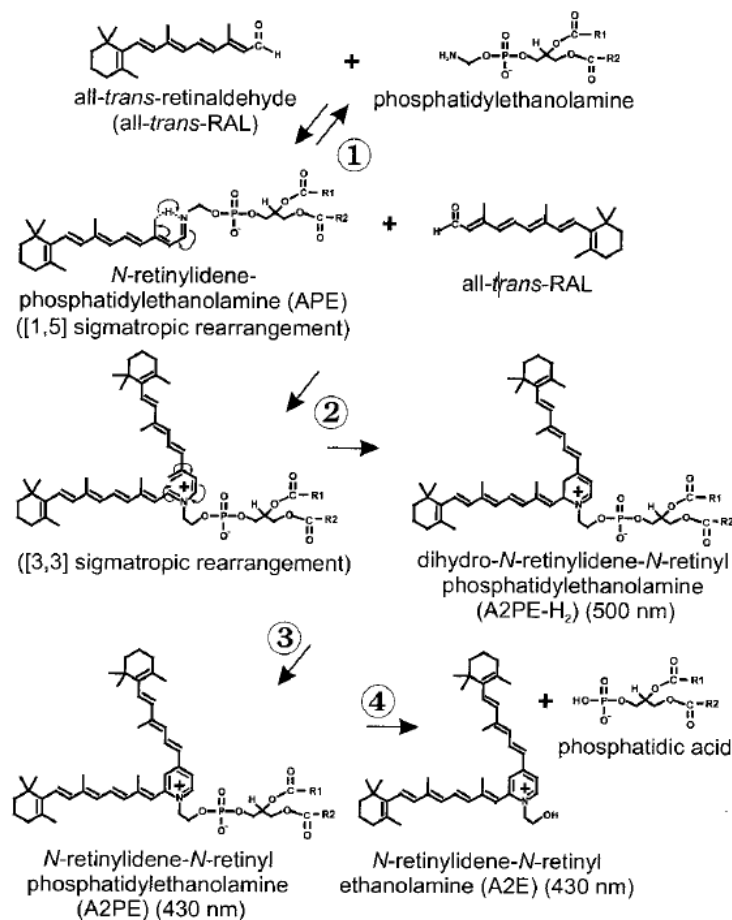
3. Overview of Mata (Exhibit 1010)

Mata studies the biosynthesis of A2E in mice and humans with ABCR-mediated retinal and macular degeneration. Ex. 1010. Mata teaches that increased lipofuscin accumulation in RPE cells is seen in “several forms

of macular degeneration” and that the toxic A2E is a major fluorophore of lipofuscin. *Id.* at 7154, Abstr. Mata teaches that the mouse *abcr* gene “encodes rim protein (RmP), an ATP-binding cassette transporter in rod outer segments,” and that “[m]ice lacking RmP accumulate A2E in RPE cells at a greatly increased rate over controls.” *Id.*

Mata identifies “three precursors of A2E in ocular tissues from *abcr*^{-/-} mice and humans with *ABCR*-mediated recessive macular degenerations” — *N*-retinylidene-phosphatidylethanolamine (APE), dihydro-*N*-retinylidene-*N*-retinylphosphatidylethanolamine (A2PE-H₂), and *N*-retinylidene-phosphatidylethanolamine (A2PE) — and suggests a biosynthetic pathway for A2E. Ex. 1010, 7154, Abstr., 7157 (right column).

Mata's Figure 5, reproduced below, illustrates its "[h]ypothetical biosynthetic pathway for A2E in mice and humans lacking the RmP transporter." Ex. 1010, 7158, Fig. 5 (caption).



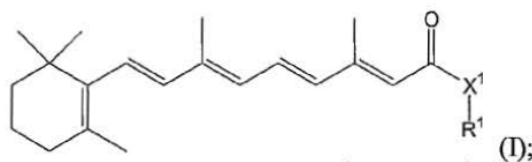
The above figure sets forth a hypothetical pathway for the biosynthesis of A2E in mice and humans lacking the RmP transporter. *Id.* Based on the proposed pathway, Mata predicted that "A2E accumulation should depend on the availability of *all-trans*-RAL [(ATR)] and hence on light exposure," and showed that the increased formation of A2E in *abcr*^{-/-} mice was blocked by raising the mice under total darkness. *Id.* at 7159, left col. Mata also suggests that "[t]he precursors of A2E identified in [its] study may represent

pharmacological targets for the treatment of *ABCR*-mediated macular degeneration” and that “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway may . . . be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.” *Id.* at Abstr., 7159 (right column).

4. Overview of Widder (Exhibit 1009)

Widder is a PCT patent publication titled “Methods and Compositions for Treating Ophthalmic Conditions with Retinyl Derivatives.” Ex. 1009, 1:1–2. Widder provides an overview of the visual cycle and teaches that toxic products, such as A2E, may “accumulate from excess production of visual cycle retinoids, such as all-*trans*-retinal (atRAL).” *Id.* at 1:12–22. Widder teaches that “the over-accumulation of toxic products is partially responsible for the symptoms associated with the macular degenerations and retinal dystrophies.” *Id.* at 1:26–28.

Widder teaches methods for reducing the formation of lipofuscin in the eye of a mammal by administering retinyl derivatives having the structure of Formula (I), reproduced below, wherein X^1 and R^1 are selected from specified groups:



Ex. 1009, 3:4–12, 3:18–20. The figure depicted above is the chemical structure of Widder’s Formula (I). Widder further teaches methods for treating ophthalmic conditions and controlling symptoms associated with such conditions, wherein the ophthalmic conditions are “macular

degenerations, macular dystrophies and retinal dystrophies” including, e.g., Stargardt Disease, recessive retinitis pigmentosa, and dry-form age-related macular degeneration. *Id.* at 2:25–28, 5:4–10.

Widder teaches that “[t]he compounds of Formula (I) can be administered in a variety of ways, including all forms of local delivery to the eye.” Ex. 1009, 25:16–17. Widder further teaches that compounds having the structure of Formula (I) may be used in combination with other treatments that have been “shown to benefit patients with macular degenerations and dystrophies,” including, for instance, certain negatively-charged phospholipids such as cardiolipin and phosphatidylglycerol. *Id.* at 33:1–5. Widder teaches that its compounds may also be used together with certain carotenoids. *Id.* at 33:8–17.

D. Alleged Obviousness

Petitioner asserts three obviousness challenges: (1) claims 1–9, 19–23, 25, 26, 28–36, 46–50, 52, and 53 over the combination of Ortho Pharma and Bergen; (2) claims 10–15, 18, 37–42, and 45 over the combination of Ortho Pharma, Bergen, and Mata; and (3) claims 16, 17, 24, 27, 43, 44, 51, and 54 over the combination of Ortho Pharma, Bergen, Mata, and Widder. Pet. 20–21. Patent Owner opposes Petitioner’s obviousness challenges. PO Resp. 14–62.

For the reasons discussed below, we determine that Petitioner has not shown by a preponderance of the evidence that any challenged claim is unpatentable.

1. Legal Standards

“In an [inter partes review], the petitioner has the burden from the onset to show with particularity why the patent it challenges is unpatentable.” *Harmonic Inc. v. Avid Tech., Inc.*, 815 F.3d 1356, 1363 (Fed. Cir. 2016); 37 C.F.R. § 42.104(b). This burden of persuasion never shifts to the patent owner. *See Dynamic Drinkware, LLC v. Nat’l Graphics, Inc.*, 800 F.3d 1375, 1378 (Fed. Cir. 2015) (discussing the burden of proof in *inter partes* review). To prevail, Petitioner must demonstrate patentability by a preponderance of the evidence. 35 U.S.C. § 316(e).

Under pre-AIA § 103, a claim is unpatentable as obvious “if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains.” 35 U.S.C. § 103(a) (2012); *see also KSR Int’l Co. v. Teleflex Inc.*, 550 U.S. 398, 406 (2007). The question of obviousness is resolved based on underlying factual determinations including: (1) the scope and content of the prior art; (2) any differences between the claimed subject matter and the prior art; (3) the level of ordinary skill in the art; and (4) any objective indicia of nonobviousness. *Graham*, 383 U.S. at 17–18. An obviousness determination based on a combination of teachings requires finding “a motivation to combine accompanied by a reasonable expectation of achieving what is claimed in the patent-at-issue.” *Intelligent Bio-Sys., Inc. v. Illumina Cambridge Ltd.*, 821 F.3d 1359, 1367 (Fed. Cir. 2016).

2. Alleged Obviousness over Ortho Pharma and Bergen

The parties dispute whether claims 1–9, 19–23, 25, 26, 28, 29–36, 46–50, 52, and 53 are unpatentable as obvious over the combination of Ortho Pharma and Bergen.

We first summarize Petitioner’s arguments and then analyze those arguments and Patent Owner’s responses. We focus on whether Petitioner has adequately demonstrated that a person of ordinary skill in the art would have had reason to combine the teachings of Ortho Pharma and Bergen to achieve the claimed invention as Petitioner proposes, with a reasonable expectation of success, as well as objective indicia of obviousness, because these issues are dispositive of all challenged claims. *Cf. Samsung Elecs. Co., Ltd. v. Elm 3DS Innovations, LLC*, 925 F.3d 1373, 1383 (Fed. Cir. 2019) (not reaching other issues where analysis of reasonable expectation of success arguments was dispositive).

*a) Overview of Petitioner’s Obviousness Argument
Based on Ortho Pharma and Bergen*

(1) Claim Limitations

Petitioner asserts that Ortho Pharma teaches or suggests all of the limitations of claims 1–9, 19–23, 25, 26, 28, 29–36, 46–50, 52, and 53, except it does not teach a retinoid that is a “substituted C₂₀-D₁₋₃” retinoid, for which Petitioner turns to Bergen. Pet. 23–39. With respect to independent

claims 28 and 29,¹⁵ for example, Petitioner asserts “Ortho Pharma discloses administering an effective amount of vitamin A in a pharmaceutically-acceptable carrier to patients in need thereof to treat a macular degeneration,” and Bergen “discloses making claimed compounds, C₂₀-D₁₋₃-retinol and C₂₀-D₁₋₃-retinol acetate, for biological studies.” *See, e.g.*, Pet. 4, 15, 21–29.

Petitioner argues that “[t]he same prior art disclosures and obviousness arguments . . . for claims 28 and 29 also render . . . obvious” claim 1, which is “identical to claim 29 except that preamble of claim 1 recites ‘retarding the accumulation of a lipofuscin pigment in a retina’ instead of ‘treating a macular regeneration.’” Pet. 29. Petitioner argues that “there is no patentable distinction between claims 29 and 1 in view of the prior art asserted,” because, based on prior art teachings regarding the deuterium kinetic isotope effect,

a POSA would have understood that employing C₂₀-deuterated vitamin A in place of non-deuterated vitamin A would have been reasonably likely to retard accumulation of A2E/lipofuscin in the retina and to treat A2E/lipofuscin-accumulation of A2E/lipofuscin in the retina and to treat A2E/lipofuscin-accumulation-associated macular degeneration.

Id. at 30 (citing Ex. 1002 ¶ 220).

¹⁵ As noted above and in the Petition, “[c]laim 29 is identical to claim 28, except that claim 29 recites that the substituted C₂₀-D₁₋₃-retinoid is in a pharmaceutical composition comprising a pharmaceutically acceptable carrier.” Pet. 27.

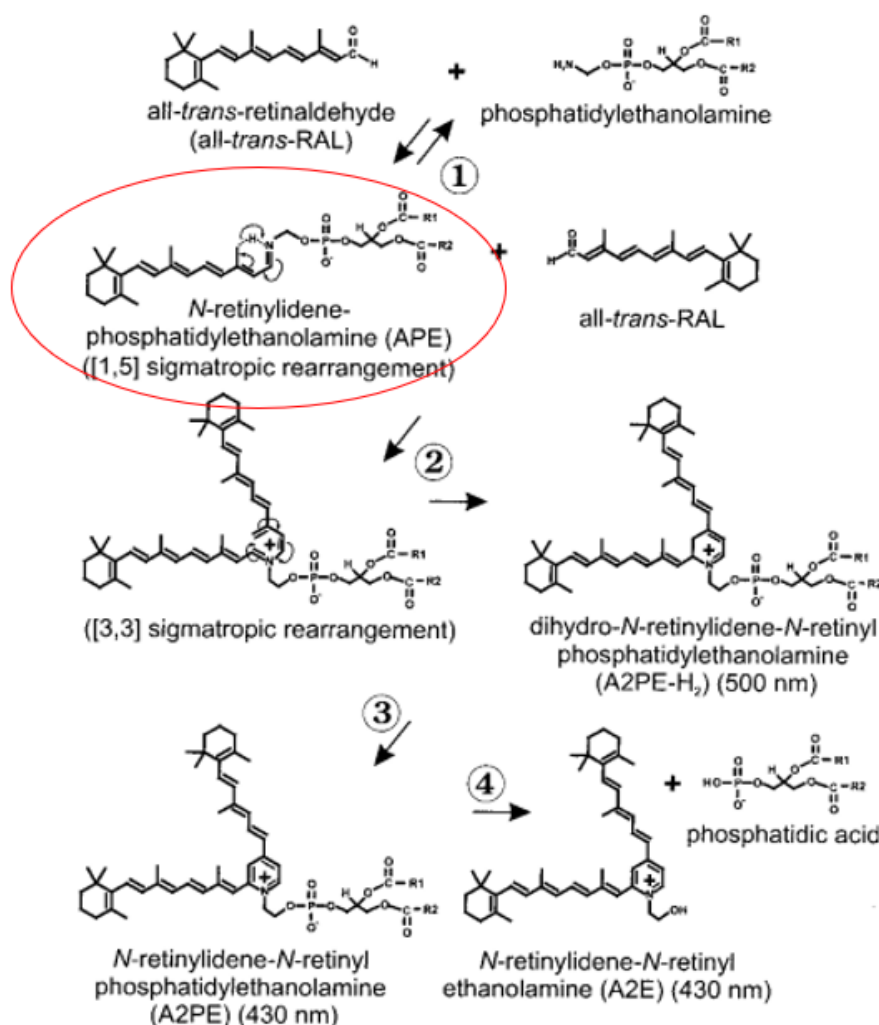
(2) Reasons to Combine

Relying on, among other things, the teachings of Mata and Dr. Guengerich's testimony, Petitioner contends that an ordinarily skilled artisan would have had reason to "replace non-deuterated forms of vitamin A being used to treat or prevent macular degeneration, as in Ortho Pharma, with C₂₀-deuterated vitamin A," such as the C₂₀-D₁₋₃-retinol and C₂₀-D₁₋₃-retinol acetate disclosed in Bergen, to arrive at methods such as that recited in claim 28. Pet. 40–41.

In particular, Petitioner argues that, by the time of the invention, an ordinarily skilled artisan would have known that (1) the visual cycle produces lipofuscin pigment A2E as a byproduct; (2) lipofuscin toxicity is associated with development of macular degeneration; (3) deprotonation at C₂₀ of retinal, which requires cleavage of a carbon-hydrogen bond, is a necessary step in A2E formation; and (4) replacing hydrogen with deuterium is useful for slowing reactions that involves cleaving a carbon-hydrogen bond. Pet. 10–12, 15, 18–19, 40–43 (citing, *e.g.*, Ex. 1010, Abstr., 7154, 7157–58, Fig. 5). Petitioner further relies on Dr. Guengerich's testimony that an ordinarily skilled artisan "would have recognized that this deprotonation [at C₂₀ of retinal] likely was a rate-limiting step in A2E formation and that substituting deuterium in place of the hydrogens at C-20 would slow A2E formation." *Id.* at 41 (citing, *e.g.*, Ex. 1002 ¶¶ 259–60).

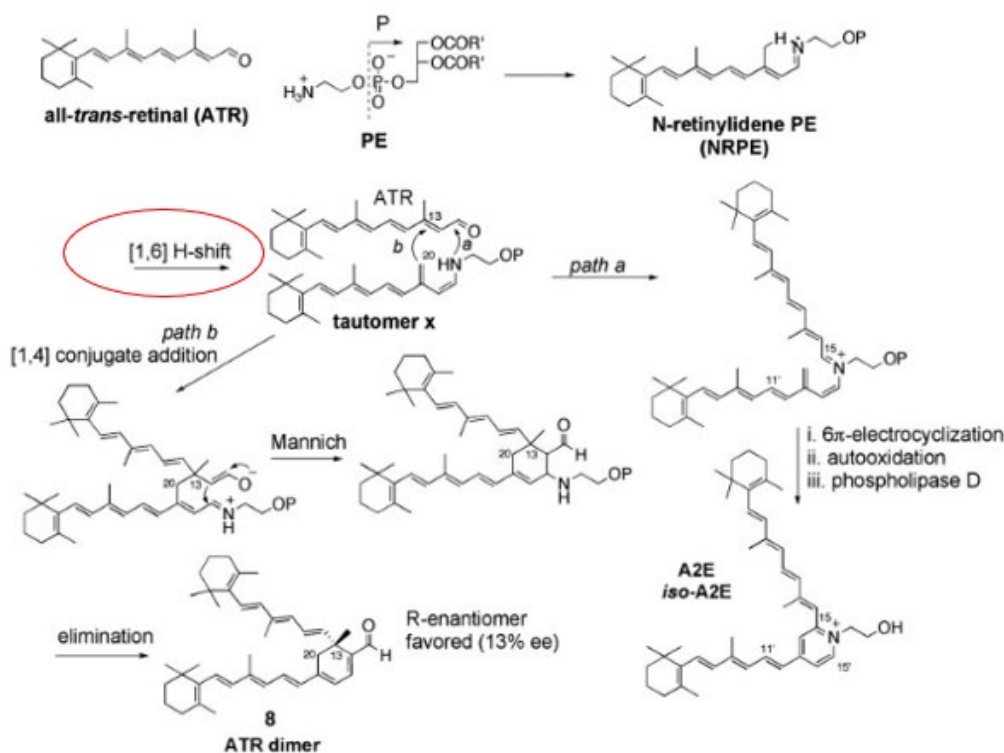
More particularly, Mata teaches that "precursors of A2E identified in [its] study may represent pharmacological targets for the treatment of ABCR-mediated macular degeneration" and that "[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway may . . . be an effective

treatment strategy for . . . macular degenerations associated with lipofuscin accumulation.” Ex. 1010, 7154 & Abstr., 7159. Petitioner argues that, based on these teachings and the proposed biosynthetic pathway for lipofuscin pigment A2E in Mata, reproduced below, an ordinarily skilled artisan would have had reason to focus on the deprotonation at C₂₀ of retinal as a way to retard lipofuscin formation. Pet. 40 (citing Ex. 1010, 7159), 42–43 (citing, *e.g.*, Ex. 1004 ¶¶ 145–148).



Ex. 1010, Fig. 5 (annotation added). The figure above depicts Mata's proposed biosynthetic pathway for A2E formation, with the step relevant to Petitioner's motivation to combine arguments circled in red. *Id.*

Dr. Guengerich further relies on the proposed biosynthetic pathway for lipofuscin pigments A2E and ATR dimer in Fishkin,¹⁶ reproduced below. Ex. 1002 ¶¶ 84–85, 98.



Ex. 1011, Fig. 10 (annotation added). The figure above depicts Fishkin's proposed biosynthetic pathway for lipofuscin pigments ATR dimer and

¹⁶ Nathan E. Fishkin et al., *Isolation and Characterization of a Retinal Pigment Epithelial Cell Fluorophore: An All-Trans-Retinal Dimer Conjugate*, 102 Proc. Nat'l Acad. Scis. 7091 (2005) (Ex. 1011, "Fishkin").

A2E, with the step relevant to Petitioner's motivation to combine arguments circled in red. *Id.*

Petitioner asserts that, in light of Mata's and Fishkin's proposed biosynthetic pathways for lipofuscin pigments, an ordinarily skilled artisan would have had reason to focus on the 1,5 sigmatropic rearrangement step¹⁷ in the A2E biosynthetic pathway, because targeting this step "would reduce undesirable lipofuscin formation without interfering with the normal function of the visual cycle" and would, furthermore, slow down the formation of both A2E and ATR-dimer, another undesirable lipofuscin chromophore.¹⁸ Pet. 42–43 (citing, *e.g.*, Ex. 1004 ¶¶ 145–148; Ex. 1002, ¶¶ 65–69, 99–1223); Ex. 1002 ¶¶ 85, 98; *see also* Reply 8, Ex. 1080 ¶ 39.

(3) Reasonable Expectation of Success

Petitioner asserts that an ordinarily skilled artisan would have had a reasonable expectation of success for administering a claimed C₂₀-deuterated retinoid to a patient to treat a macular degeneration (claims 28 and 29) or to retard accumulation of a lipofuscin pigment in a retina (claim 1). Pet. 43.

Petitioner first argues that, as evidenced by Bergen and Ortho Pharma, both the claimed C₂₀-deuterated vitamin A and "compositions formulating

¹⁷ The 1,5 sigmatropic rearrangement is also sometimes referred to as the 1,5-shift or the [1,5]-shift by the parties and/or in this Decision.

¹⁸ Arguments regarding C₂₀-deprotonation's role in the formation of ATR-dimer, another lipofuscin pigment, and its relevance to motivation to combine, do not appear to have been made explicitly in the Petition. However, because these arguments were predicated on Dr. Guengerich's declaration submitted with the Petition, we include them in this Decision.

vitamin A (including deuterated forms of vitamin A) in a pharmaceutically acceptable carrier were known in the art.” Pet. 43–44.

Petitioner further argues that Ortho Pharma also teaches administering vitamin A to treat or prevent macular degeneration. Pet. 44. Relying on the declarations of Drs. Guengerich and Calman, Petitioner next argues with respect to the use of C₂₀-deuterated vitamin A in the claimed methods that “literature amply supported [a] reasonable expectation that C₂₀-deuteration of vitamin A would slow A2E/lipofuscin formation by 5-10 times,” and an ordinarily skilled artisan “would have recognized . . . the desirability of this expected slowing of A2E/lipofuscin formation for patients in need of treatment for . . . macular degeneration.” Pet. 45 (citing, *e.g.*, Ex. 1002 ¶¶ 99–123; Ex. 1004 ¶¶ 143–144).

Finally, Petitioner argues that “the reasonable expectation of success is not subject to reasonable dispute because the ’045 patent admits that formulation of the claimed compounds was conventional and within the skill of the art” and that “C₂₀-deuterated retinoids, when administered to a patient, can ‘retard[] formation of a lipofuscin pigment in the retina’” and treat diseases such as macular degeneration. Pet. 45–46.

b) Analysis of Motivation to Combine and Reasonable Expectation of Success

We analyze motivation to combine and reasonable expectation of success together because, although they are separate requirements, they are intertwined under the facts of this particular case. *See, e.g., Alza Corp. v. Mylan Labs., Inc.*, 464 F.3d 1286 (Fed. Cir. 2006) (explaining that the issues in the case “reduce essentially” to whether

one of ordinary skill in the art would have reasonably expected the claimed drug formulation to have therapeutic value and thus be motivated to produce it).

Considering all of the arguments and evidence of record, we find that Petitioner has not adequately demonstrated that a person of ordinary skill in the art would have been motivated to combine Ortho Pharma and Bergen in the manner Petitioner proposes, with a reasonable expectation of success of arriving at a method of “retarding the accumulation of a lipofuscin pigment in a retina,” as recited in claim 1, or of “treating a macular degeneration,” as recited in claims 28 and 29.

As an initial matter, we agree with Patent Owner that the prior art teachings that (1) “[t]he precursors of A2E identified in [Mata] may represent pharmacological targets for the treatments of *ABCR*-mediated macular degeneration” and (2) “[p]harmacologic inhibition of one or more steps in the A2E synthetic pathway may . . . be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation” do not, by themselves, render obvious the claimed methods of retarding lipofuscin accumulation or treating macular degeneration. Ex. 1010, 7154 & Abstract, 7159. For instance, although there were only a limited number of A2E precursors identified in Mata, there were no suggestions of which specific precursor or step in the biosynthetic pathway to target, or what particular form the pharmacological inhibition should take. In short, these statements in Mata “at best give[] only general guidance as to the particular form of the claimed invention or how to achieve it,” and in

those circumstances “relying on an obvious-to-try theory to support an obviousness finding is impermissible.” *Leo Pharm. Prod., Ltd. v. Rea*, 726 F.3d 1346, 1356 (Fed. Cir. 2013) (quoting *In re Cyclobenzaprine Hydrochloride Extended-Release Capsule Patent Litigation*, 676 F.3d 1063, 1073 (Fed. Cir. 2012)).

However, as discussed above, Petitioner also has submitted evidence in this case, in the form of Dr. Guengerich’s testimony, why an ordinarily skilled artisan would have recognized, based on its location in the A2E biosynthetic pathway, that the 1,5-shift in NRPE¹⁹ was a particularly desirable point in the pathway for intervention to retard lipofuscin accumulation. *See, e.g.*, Reply 8 (citing Ex. 1002 ¶¶ 84, 85, 93–98, 184). Dr. Guengerich testifies that an ordinarily skilled artisan further would have been motivated to substitute C₂₀-deuterated vitamin A in place of vitamin A in Ortho Pharma’s disclosed methods of treating macular degeneration, because such an artisan would have recognized that deuteration would slow deprotonation, a requisite step in A2E formation, which would be

¹⁹ According to Dr. Guengerich, the chemical structure labeled as APE in Mata’s Figure 5 is likely a compound in “a transition state [rather] than the individual compound” before or after the 1,5 sigmatropic rearrangement.” Ex. 2103, 77:6–24, 84:19–87:15. That is, it shows “the hydrogen bonded to . . . both [the] nitrogen and the carbon.” *Id.* at 85:13–86:2. In this Decision, APE and NRPE may refer to the compound before and/or after the 1,5-shift, or the transition state, depending on the context of the discussion. References to “activated NRPE,” a term used by Dr. Guengerich in his Reply Declaration, are to [1,5]-shifted NRPE, which reacts with ATR to form A2PE-H₂ (after a [3,3] sigmatropic rearrangement) in Mata’s proposed A2E biosynthetic pathway. Ex. 1080 ¶ 53; Ex. 1010, 7158, Fig. 5.

“reasonably likely to retard accumulation of A2E/lipofuscin in the retina and to treat A2E/lipofuscin-accumulation-associated macular degeneration.” Pet. 30 (citing, *e.g.*, Ex. 1002 ¶ 220), 41–43.

Because we “take account of the inferences and creative steps that a person of ordinary skill in the art would employ” in an obviousness analysis, we give some weight to Dr. Guengerich’s testimony. *KSR*, 550 U.S. at 418; *Plantronics, Inc. v. Aliph, Inc.*, 724 F.3d 1343, 1354 (Fed. Cir. 2013) (explaining that “motivation to combine may be found. . . in . . . the background knowledge, creativity, and common sense of the person of ordinary skill”).

Nevertheless, even if we were to agree that an ordinarily skilled artisan would have seen the 1,5-shift in NRPE in Mata’s A2E biosynthetic pathway as a particularly desirable location for intervention, we are not persuaded that such a person would have been motivated to substitute C₂₀ deuterated vitamin A for the vitamin A in OrthoPharma’s composition and method, because Petitioner has not shown, by a preponderance of evidence, that such an artisan would have reasonably expected the substitution to retard the accumulation of A2E or to treat macular degeneration.

Petitioner largely relies on Dr. Guengerich’s testimony to argue that a POSA would have reasonably expected replacing vitamin A in OrthoPharma’s method with a C₂₀-deuterated version to “slow A2E formation due to the powerful, primary kinetic isotope effect expected from these substitutions.” Pet. 41. More particularly, Petitioner argues that (1) inhibiting the 1,5-shift, the “first step” of A2E biosynthesis, will result in less reactants for subsequent reactions and thus result in less A2E, the final

product, “regardless of how slow or fast” subsequent reactions are; and (2) “the 1,5-shift was slow enough under physiological conditions to be rate-limiting, because ‘forced’ conditions were required to expedite” the step. Reply 6, 7–8 (citing, *e.g.*, Ex. 2103, 58:2–12, 63:19–25, 121:6–123:12; Ex. 1080 ¶¶ 20, 52–53). Petitioner argues that Roth,²⁰ Itou,²¹ and Doering²² “corroborated both the 1,5-sigmatropic rearrangement’s specific slowness and its large expected KIE.” *Id.* at 8.

(1) *Rate-limiting*

Because there is some confusion over the parties’ use of the term “rate-limiting,” we first clarify this concept for purposes of our analysis. As noted above, Petitioner argued, as its reason to combine Bergen and Ortho Pharma, that an ordinarily skilled artisan “would have recognized that [the] deprotonation [at C₂₀ of NRPE] likely was a rate-limiting step in A2E formation and that substituting deuterium in place of the hydrogens at C-20 would slow A2E formation.” Pet. 41 (citing, *e.g.*, Ex. 1002 ¶¶ 259–60).

With respect to the “rate-limiting” step, Dr. Prestwich states as

²⁰ Roth & König, *Hydrogen Displacements, IV: Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in Cis-Pentadiene-(1.3)*, 699 ANNALS OF CHEMISTRY 24 (1966) (Ex. 1015, “Roth”).

²¹ Itou et al., *Quantum Treatment of Hydrogen Nuclei in Primary Kinetic Isotope Effects in a Thermal [1,5]-Sigmatropic Hydrogen (or Deuterium) Shift from (Z)-1,3-Pentadiene*, 111 J. PHYSICAL CHEMISTRY A 261 (2007) (Ex. 1016, “Itou”).

²² William von E. Doering & Xin Zhao, *Effects on Kinetics by Deuterium in the 1,5-Hydrogen Shift of a Cisoid-Locked 1,3(Z)-Pentadiene, 2-Methyl-10-methylenebicyclo[4.4.0]dec-1-ene: Evidence for Tunneling?*, 128 J. AM. CHEM. SOC’Y 9080 (2006) (Ex. 2025, “Doering”).

follows in his declaration:

Fundamental principles of chemical kinetics dictate that in multistep chemical reactions the overall rate of product formation is generally determined by the “rate-limiting” step. This rate-limiting step, also known as the slowest step, the bottleneck, or the rate-determining step, acts as a control point in the reaction sequence.

Faster steps before or after the rate-limiting in a multistep chemical reaction do not significantly influence the overall reaction rate, as the system can only proceed as quickly as its slowest component allows.

Ex. 2052 ¶¶ 50–51.

Dr. Guengerich similarly explains his concept of “rate-limiting” in his deposition:

When you have a series of reactions, which they’re in linear array or a cyclic array, the rate-limiting step – a rate limiting – a rate-limiting step will be the slowest one. Now, that doesn’t have anything to say about how much rate limiting it is compared to other steps. And you may have more than one rate-limiting step too.

So it is a qualitative statement – well, it depends on quantitative numbers, but it’s a bit of a qualitative term.

Ex. 2209, 53:21–54:8.

Patent Owner contends that “Dr. Guengerich disavowed — and Petitioner does not rehabilitate — his core premise that ‘the (1,5)-sigmatropic rearrangement *is likely to be the rate-limiting step*’” Sur-reply 2. Petitioner contends Patent Owner’s argument hinges on the erroneous assertion that “the 1,5-shift must be *the* slowest step to be a rate-limiting step” and that Dr. Guengerich did not abandon the argument in the Petition that an ordinarily skilled person would have recognized that the 1,5-

shift is likely *a* rate-limiting step, i.e., that “C₂₀-deuteration likely *would* inhibit the A2E-biosynthetic pathway.” Reply 5–6 (citing, *e.g.*, Ex. 1080 ¶¶ 16–19), 7. Petitioner asserts “[t]here is no absolute requirement that there be only a single, slowest rate-limiting step”; accordingly, “calculating rates” of different steps in the A2E biosynthetic pathways was not required. *Id.* at 7 (citing Ex. 1080 ¶¶ 21–25).

We agree with Petitioner that Petitioner’s obviousness case does not depend on it showing that the 1,5-shift is the *only* rate-limiting step in the A2E biosynthetic pathway or to explicitly calculate the rates of each of the different steps in the pathway. Nevertheless, to succeed on the obviousness case put forth in its Petition, Petitioner must show by a preponderance of evidence that an ordinarily skilled artisan would reasonably expect C₂₀-deuteration of retinal to retard the accumulation of A2E and/or treat macular degeneration.²³ Having weighed the evidence submitted by the

²³ Patent Owner asserts Dr. Guengerich’s argument that slowing down any step in the A2E biosynthetic pathway will be reasonably expected to retard lipofuscin accumulation is new and should be disregarded. Sur-reply 2–3. We acknowledge that Petitioner has added significant details to its obviousness theory post-institution, including explaining the *reason* Petitioner asserts this the 1,5-shift to be a “rate-limiting” step in A2E formation – i.e., because it determines the concentration of the starting reactants of the biosynthesis. However, we need not decide whether Petitioner has satisfied the particularity requirement of 35 U.S.C. § 312 (a)(3). As discussed below, we find that Petitioner has not met its burden of showing the challenged claims to have been obvious even when we consider all of the arguments Petitioner has made at trial.

parties, and for the reasons discussed below, we are not persuaded that Petitioner has met its burden.

(2) Reasonable expectation that C₂₀ deprotonation of retinal is a rate-limiting step

Relying on Dr. Guengerich’s testimony, Petitioner asserts that “Mata presented information sufficient to reasonably expect the 1,5-shift was *a* rate-limiting step that was desirable to inhibit.” Reply 7 (citing Ex. 1080 ¶¶ 25–27, 28–40); *see also id.* at 14 (asserting that “[p]rior-art disclosure that the 1,5-shift ‘unleashes the conversion of the essential vitamin A nutrient into a toxic and undesirable byproduct’ was enough reason to use C₂₀-deuteration to inhibit it”) (quoting Ex. 1080 ¶ 48), 17 (arguing that, “[b]ecause of the 1,5-shift’s location in the disclosed pathway, inhibiting that step was reasonably expected to reduce A2E/lipofuscin formation, providing a treatment for [macular degeneration]”) (citing Ex. 1080 ¶¶ 16–20).

As noted above, Petitioner argues that (1) inhibiting the 1,5-shift will result in less A2E, the final product, “regardless of how slow or fast” subsequent reactions are; and (2) as corroborated by Roth, Itou, and Doering, “the 1,5-shift was slow enough under physiological conditions to be rate-limiting.” *Id.* at 6, 7–8 (citing, *e.g.*, Ex. 2103, 58:2–12, 63:19–25, 121:6–123:12; Ex. 1080 ¶¶ 20, 52–53). We address each of these arguments below.

Reduction of Reactant Concentration

Evidence of record shows an ordinarily skilled artisan would reasonably expect the rate of bimolecular condensation reaction between NRPE and ATR that results in A2PE-H₂ — and eventually results in A2E formation — depends on both reactant concentration and the rate of reaction. Ex. 2052 ¶¶ 198–199; *see also* Reply 6–7 (citing, *e.g.*, Ex. 1080 ¶¶ 22–24; Ex. 2052 ¶¶ 104, 110, 184, 198).

As an initial matter, however, Petitioner and Dr. Guengerich do not persuasively explain why an ordinarily skilled artisan would reasonably expect that using C₂₀-deuterated vitamin A in Bergen’s composition would *reduce* the concentration of “activated” NRPE (i.e., NRPE after the 1,5-shift) sufficiently to retard lipofuscin formation or treat macular degeneration in a patient, when Bergen teaches using its composition as a supplement (i.e., as an *additional* source of vitamin A). PO Resp. 17–21;²⁴ Ex. 2052 ¶ 244, n.58.

²⁴ Patent Owner frames its argument as one of teaching away. PO Resp. 17–21. Petitioner argues that “[t]he petition proposed substituting C₂₀-deuterated vitamin A for the prior-art vitamin A administered to [macular degeneration] patients” and that “PO identifies no teaching away from this proposed combination.” Reply 2 (emphasis omitted). Even if prior art teachings do not rise to the level of teaching away, however, such teachings may nevertheless be relevant to motivation to combine. *See, e.g., Polaris Indus., Inc. v. Arctic Cat, Inc.*, 882 F.3d 1056, 1069 (explaining that, “even if a reference is not found to teach away, its statements regarding preferences are relevant to a finding regarding whether a skilled artisan would be motivated to combine that reference with another reference”).

In this regard, we acknowledge Petitioner’s argument that during prosecution Patent Owner had asserted that, “[b]ecause it is well accepted in the art that replacement of hydrogen with this isotope material will no[t] generally affect the ability of the substituted compounds to interact with proteins, a person of ordinary skill in the art would immediately conclude . . . that C20-D3 vitamin A will be used as natural substrates [in the visual] cycle and not cause any side effects in the patient.” Tr. 55:25–56:14 (citing Pet. 43); *see also* Ex. 1031, 117. However, in the context of the rejection, the statement responds to Examiner’s assertion that Patent Owner had “failed to provide an enabling disclosure to show *lack of side effects*” (Ex. 1031, 116 (emphasis added)); thus, we are not persuaded it suggests that an ordinarily skilled artisan would have reasonably expected C₂₀-deuterated vitamin A to retard lipofuscin accumulation or treat macular degeneration independent of the remaining disclosures in the patent application. Ex. 1031, 116–117.

We also acknowledge Dr. Guengerich’s testimony that “[m]any macular degeneration patients already were taking vitamin A supplements,” that several studies involved patients taking high levels of vitamin A for prolonged periods of time without incident, that “[d]ietary sources of vitamin A often were less readily available for absorption,” and that “the body carefully regulates the plasma concentration of vitamin A.” Ex. 1080 ¶¶ 74–77. We further acknowledge his conclusion that, based on the above, a “POSA would have recognized that replacing existing vitamin A sources with C₂₀-deuterated vitamin A would be reasonably likely to advantageously reduce A2E/lipofuscin formation.” *Id.* ¶ 77.

Nevertheless, we weigh Dr. Guengerich's testimony and the evidence cited by Petitioner in this regard with other evidence of record. Petitioner's expert Dr. Calman testified that "avoiding excess dietary vitamin A is the recommendation specifically for Stargardt's," because "basically, the more substrate you're inputting into the visual cycle, potentially that's exacerbating the buildup of ATR, which is the lipofuscin precursor." Ex. 2104, 14:1–22, 17:17–22:6. Although Stargardt's involves a specific genetic mechanism as compared to macular degeneration generally, Dr. Calman's testimony suggests that an ordinarily skilled artisan expected increasing vitamin A intake to increase the amount of vitamin A that reaches the eye at least to some degree, because the specific genetic defect in Stargardt's disease affects "a *photoreceptor*-specific adenosine triphosphate (ATP)-binding cassette transporter." Ex. 1001, 2:26–30 (emphasis added); Ex. 1050, 2960, Fig. 1.

Similarly, in the context of unexpected results, Patent Owner's expert Dr. Del Priore testified that it was surprising that C₂₀-deuterated vitamin A can quickly replace "normal vitamin A stores" in the eye, both because vitamin A has a long half-life of 140 days in the body and is "notoriously hard" to deplete in the retina and because the many dietary sources of vitamin A and provitamin A carotenoids makes limiting the intake of non-deuterated vitamin A difficult. Ex. 2192 ¶ 316.

Having weighed the evidence above, we are not persuaded Petitioner has shown by a preponderance of evidence that a person of ordinary skill would have reasonably expected C₂₀-deuterated vitamin A supplements to reduce the concentration of "activated" NRPE—which according to Mata

results from a reaction between vitamin A/ATR and phosphatidylethanolamine (PE)—sufficient to retard lipofuscin formation or treat macular degeneration, including Stargardt’s disease. *See generally* PO Resp. 16–24. Although Dr. Guengerich asserts that “Dr. Prestwich provides no reason to assume that maintaining sufficient vitamin A plasma levels using C₂₀-deuterated vitamin A as a replacement for non-deuterated sources of vitamin A . . . would fail to reduce A2E formation as compared to the status quo,” Ex. 1080 ¶ 74, the burden to show unpatentability rests with Petitioner.

Rate-Limiting Reaction

Furthermore, to the extent an ordinarily skilled artisan would have expected administering C₂₀-deuterated vitamin A to decrease the “activated” form of NRPE, asserted to be one of the two reactants to the bimolecular condensation reaction, we are not persuaded that Petitioner has shown, by a preponderance of evidence, that such a person would reasonably expect the decrease to retard accumulation of lipofuscin *regardless of the rates of other steps in A2E formation*.

First, although Dr. Guengerich states in his Rebuttal Declaration that “the phosphatidyl analogue of enamine (via C₂₀-deuteration) is the limiting reactant,” he cites as support only Dr. Prestwich’s alleged testimony that “ATR concentrations in the disc space of the photoreceptor outer segment were elevated.” Ex. 1080 ¶ 42 (citing Ex. 2052 ¶¶ 197–206). To the extent

Dr. Guengerich is referring Dr. Prestwich's quotation from Sparrow²⁵ that "[t]he reaction of NRPE with a second all-*trans*-retinal to form a molecule of A2-PE" is likely to occur "probably only when circumstances, including high levels of illumination, increase the availability of [ATR]" (Ex. 2052 ¶ 202 (quoting Ex. 1033, 2)), Dr. Guengerich's conclusory statement does not explain why a reaction that is likely to occur only when availability of ATR is increased indicates that it is the other reactant that is limiting. *Id.*

Likewise, although Dr. Guengerich states that "[r]educing the concentration of the limiting reactant (in this case, inhibiting the [1,5]-shift) would predictably slow the [bimolecular] condensation and the downstream, irreversible, and undesirable formation of dihydro-A2PE more potently and easier than reducing ATR concentrations," Dr. Guengerich does not persuasively address the references cited by Dr. Prestwich suggesting that, *at the time of the invention*, those of ordinary skill in the art believed it is the availability of ATR — which is needed both to form the NRPE as well as to react with the NRPE to form A2PE-H₂ — that is the limiting reactant. Ex. 1080 ¶ 42; Ex. 2052 ¶¶ 113, 200; *see also, e.g.*, Ex. 1010, 7159 (predicting and confirming that "A2E accumulation should depend on the availability of all-*trans*-RAL"); Ex. 2003, 35, Fig. 5 caption (stating that "[p]harmacological interventions that reduce light-dependent formation of all-*trans*-RAL greatly reduce the probability of [a secondary condensation between NRPE with another all-*trans*-RAL] and inhibit formation of A2E").

²⁵ Janet R. Sparrow, *A2E, a Byproduct of the Visual Cycle*, 43 VISION RSCH. 2983 (2003).

In this regard, Dr. Guengerich also testified that he is not aware of the concentrations of ATR in the cells of the eye. Ex. 2103, 65:22–69:4.

As another example, Dr. Prestwich notes that Mata also identified, as a pre-requisite to A2E formation, transport of A2PE-H2 from the rod outer segment to RPE via phagocytosis. Ex. 2052 ¶¶ 212–213. Dr. Prestwich testifies that, based on prior art available before 2007, an ordinarily skilled artisan “would have understood this transport step [as] a discontinuous biological process” with a rate “independent of the rate of the prior chemical reaction steps” and that “[t]his discontinuous step is more likely [than the 1,5-shift] to be rate-limiting.” *Id.* ¶ 215. Dr. Prestwich analogized “the periodic and discontinuous nature of phagocytosis [as] like a ferry transporting cars from one road on a mainland to a road on an island” and that, “[i]n general, even a slowdown in traffic on the way to a ferry will not impact the overall trip time if the wait for the ferry takes a much longer time than other parts of the trip.” *Id.*

In reply, Petitioner relies on Dr. Guengerich’s testimony to support the argument that, “regardless of the A2PE-to-A2E conversion rate or the RPE cell-phagocytosis rate. . . , inhibiting the 1,5-shift would reduce the amount of A2PE and the resulting A2E concentration.” Reply 9–10 (citing Ex. 1080 ¶¶ 43–45). However, Dr. Guengerich’s testimony on this topic is once again conclusory, stating only that, regardless of Dr. Prestwich’s analogy to phagocytosis as a rate-limiting “ferry,” “a POSA would have recognized that the key to inhibiting A2E/lipofuscin formation was slowing the [1,5]-shift.” Ex. 1080 ¶ 45.

To the extent Dr. Guengerich provided a rationale for his conclusion, that rationale appears to be that “[a] build-up of higher concentrations of dihydro-A2PE [(i.e., A2PE-H₂)] in the outer segments was undesirable, even if Dr. Prestwich were correct that RPE phagocytosis of those outer segments was periodic like a car ferry.” *Id.* But this argument does not address Dr. Prestwich’s point, i.e., that an ordinarily skilled artisan would not have reasonably expected C₂₀-deuterated retinal to retard *lipofuscin* (i.e., A2E) accumulation or treat macular degeneration, if they would have understood the transport step, rather than the [1,5]-shift, to be the rate-limiting step in A2E biosynthesis.²⁶ Indeed, when asked to confirm that “it doesn’t matter . . . to [his] opinion where each substep in Mata Figure 5 occurs within the eye’s cellular compartment,” Dr. Guengerich states that, “it’s probably more complicated than that because it would actually matter about *the rates at*

²⁶ That is, a “[a] build-up of higher concentrations of dihydro-A2PE in the outer segments” may indeed be undesirable, but missing from this explanation is why the build-up would lead to slower accumulation of lipofuscin after phagocytosis. In a separate part of his Rebuttal Declaration, Dr. Guengerich asserts that Dr. Prestwich’s testimony that “A2E will not be found in the RPE unless the RPE cell phagocytose the photoreceptor outer segments . . . has very little relevance” because, “[b]y the time phagocytosis comes into play, the conversion of NRPE and the bimolecular condensation have already placed the molecule of ATR irreversibly on the path to becoming A2E.” Ex. 1080 ¶ 71. Once again, however, this rebuttal does not squarely address Dr. Prestwich’s point that an ordinarily skilled artisan would not have reasonably expected slowing down the 1,5-shift to retard lipofuscin accumulation if the *rate* of phagocytosis is significantly slower than that of the other steps in A2E biosynthesis.

which they move to other compartments and if there were any alternative fates for those.” Ex. 2103, 115:17–21 (emphasis added).²⁷

Petitioner asserts “Dr. Prestwich proposed inhibiting A2E formation by reducing vitamin A concentrations to reduce downstream concentrations of all-*trans*-retinal, even though all-*trans*-retinal creation is a very rapid, light-catalyzed reaction,” and further “proposes inhibiting still other enzymes that he does not claim are rate-limiting.” Reply 7 (citing, *e.g.*, Ex. 1080 ¶ 23; Ex. 2052 ¶¶ 50, 56, 76, 84, 116). Petitioner argues this supports the proposition that an ordinarily skilled artisan would have reasonably expected inhibiting 1,5-shift to retard lipofuscin formation regardless of the rates of other steps of A2E biosynthesis.

We are not persuaded. First, it is Petitioner’s burden to show that a person of ordinary skill in the art would have had reasonable expectation of success. Patent Owner’s argument that an ordinarily skilled artisan may not have had such reasonable expectation, because they would have expected other steps in the pathways to be rate-limiting, does not shift this burden from Petitioner. Second, Dr. Prestwich’s argument that an ordinarily skilled artisan would have expected ATR concentration to be rate limiting for

²⁷ Dr. Calman’s testimony cannot support Petitioner’s obviousness case with respect to the issues discussed above. As Dr. Calman has explained, even though he had an understanding of deuteration and its *general* effects on reaction rates, he deferred to Dr. Guengerich on “when a deuteration would or would not have an effect on a particular reaction.” Ex. 2104, 73:6–79:1, 98:21–99:6.

purposes of A2E synthesis is based on disclosures in the art. Ex. 2052 ¶¶ 113 (citing, *e.g.*, Ex. 1010), 200 (citing, *e.g.*, Ex. 2003).

Slowing reaction due to large kinetic isotope effect

We are likewise unpersuaded by Petitioner's argument that the "large KIE reported in Roth and Itou" supports its assertions that an ordinarily skilled artisan would reasonably have expected 1,5-shift to be slow enough to be a rate-limiting step in A2E biosynthesis. Reply 11. Petitioner relies on Dr. Guengerich's testimony that "a POSA would have understood deuterating C₂₀ would slow A2E formation because 1,5-sigmatropic shifts were known to be subject to strong primary deuterium KIEs." Pet. 42 (citing Ex. 1002 ¶¶ 262, 99–123; Ex. 1015; Ex. 1016, 261–67). However, evidence of record supports Patent Owner's argument that the degree of observed KIE in a multi-step reaction depends on the rate of other steps in the reaction. Ex. 1013, 114 (explaining that "[i]n multistep enzymatic process . . . many factors may influence, or 'mask,' [the] intrinsic isotope effect and thus observed (or 'apparent') kinetic deuterium isotope effects are normally much smaller" than the intrinsic isotope effect);²⁸ Ex. 1014, 385 (stating that

²⁸ At certain points during trial, Dr. Guengerich appears to distinguish between enzymatic and "linear" reactions to argue that, in contrast to "cyclic" multi-step enzymatic reactions where "one [step] can slow down the overall rate of reaction," in a linear reaction blocking any step of the reaction will slow down the production of the final product. Ex. 2103, 64:6–14. However, evidence of record suggests that, whether a reaction is enzymatic or linear, "kinetic isotope effect obtains only when a bond to a

“[p]rimary kinetic isotope effects are operative when cleavage of the bond to the heavy isotope is the rate-limiting step in the reaction”); PO Resp. 43 (citing Ex. 2085, 1, 7; Ex. 2083, 1; Ex. 2084, 3; Ex. 1013, 34; Ex. 2052 ¶ 262). As discussed above, we are not persuaded that Petitioner has shown an ordinarily skilled artisan would have reasonably expected the 1,5-shift in NRPE to be a rate-determining step for A2E formation regardless of the other steps in the pathway.

We find Petitioner also has not persuasively shown that an ordinarily skilled artisan would have reasonably expected the calculated KIE in Roth, Itou, and Doering to apply to the 1,5-shift in Mata’s A2E biosynthetic pathway. As Patent Owner points out, and Dr. Guengerich acknowledged, these references used “a simplified, symmetric hydrocarbon” that is structurally different from NRPE, “an asymmetric molecule having nitrogen.” Ex. 2103, 74:15–75:16.

Petitioner argues that the structural dissimilarity between cis-pentadiene discussed in Roth does not undermine the motivation for combining Bergen and Ortho Pharma to arrive at the claimed methods, with a reasonable expectation of success. Reply 12. In particular, Petitioner asserts that “*structural asymmetry* of a molecule” should not be conflated with “a non-symmetrical *transition state*.” *Id.*

Dr. Guengerich explained that symmetry in the transition state refers

hydrogen atom is broken (or formed) in the rate-controlling step of a reaction,” Ex. 2084, 267, and we credit Dr. Prestwich’s testimony to this effect. Ex. 2052 ¶¶ 129–138.

to “similarity of the distance between the product and the transition state with the starting material and the transition state.” Ex. 2209, 13:13–22. We agree it is the symmetry of the transition state that determines the degree of KIE. Nelson²⁹ explains, for instance, that

[t]he intrinsic primary isotope effect . . . for a reaction is the magnitude of the isotope effect on the rate constant for the bond-breaking step (C–H versus C–D) of the reaction and is related to the symmetry of the transition state for that step. The larger the isotope effect, the more symmetrical the transition state

Ex. 2085, 1.

Nevertheless, we are not persuaded by Petitioner’s arguments: Dr. Guengerich testified that, in “purely chemical reactions” as well as those involving enzymes, there are many “factors [that] can influence the distance between the product and the transition state with the starting material,” including the composition of the molecules, and that “it’s not readily predictable.” Ex. 2209, 14:5–16:19. Although Dr. Guengerich asserts in his Rebuttal Report that, “based on Mata’s identification of the NRPE reaction as a [1,5]-sigmatropic rearrangement, a POSA would have recognized that the transition state of the reaction was likely to be symmetrical” and that molecules “analogous” to NPPE “well known in the art to be prone to strong KIEs,” Ex. 1080 ¶ 57, he cites to no corroborating references to support his assertions and provides no explanation to bolster his conclusions.

²⁹ Sidney D. Nelson & William F. Trager, *The Use of Deuterium Isotope Effects to Probe the Active Site Properties, Mechanism of Cytochrome P450-Catalyzed Reactions, and Mechanisms of Metabolically Dependent Toxicity*, 31 Drug Metabolism & Disposition 1481 (2003) (Ex. 2085, “Nelson”).

Accordingly, though we have considered his testimony on this point, we do not give it significant weight, especially in view of his deposition testimony that transition states are not readily predictable and are affected by many factors.

Petitioner argues that Patent Owner's "masking argument is 'speculative' and 'at most goes to the degree of the KIE that would be observed' rather than whether A2E/lipofuscin formation would slow." Reply 13; *see also id.* at 17 (citing Ex. 1080 ¶¶ 52–54). Petitioner similarly contends that Patent Owner's arguments "require exaggerated biological complexity that ignores the straightforward task of inhibiting the slow but undesirable [NRPE] modification in the disc interior." *Id.* at 13 (citing Ex. 1080 ¶¶ 65–71). Petitioner argues that "[t]he prior art suggested specifically inhibiting the A2E-byproduct pathway rather than the visual cycle, so unresolved visual-cycle questions are irrelevant," and steps known to occur *after* irreversible A2PE-H₂ formation merely "distract from inhibiting the 1,5-shift (known to unleash biomolecular condensation)." *Id.* (citing Ex. 1080 ¶¶ 66, 68, 71)

For the reasons discussed above, we are not persuaded that Patent Owner's arguments are speculative or that they do not go to the issue of whether a person of ordinary skill would have reasonably expected administering a deuterated vitamin A to retard lipofuscin accumulation. Neither are we persuaded by Petitioner's arguments that Patent Owner's arguments do not preclude motivation and reasonable expectation of success because of the simplicity of performing a KIE study. Reply 13. Obviousness requires that an ordinarily skilled artisan would have been

motivated to make a combination, not merely whether the combination could have been made. *Virtek Vision Int’l ULC v. Assembly Guidance Sys., Inc.*, 97 F.4th 882, 886–87 (Fed. Cir. 2024). Without showing that an ordinarily skilled artisan would have reasonably expected administering a deuterated vitamin A to retard lipofuscin accumulation, Petitioner has not shown that such a person would have been motivated to perform the KIE study under the theory of obviousness advanced in its Petition. Reply 13.

Finally, Petitioner argues Patent Owner “cannot . . . repudiate its admissions” in the ’045 patent that “efficacy naturally results from C₂₀-deuterium substitution” and that “dosing, formulation, and administration means (including oral) all were routine and within the POSA’s skill.” Reply 16. Petitioner argues that Mata and Fishkin “provided good reason to inhibit the 1,5-shift *before* the ’045 patent,” and “[n]oting patentee admissions about . . . properties inherent to C₂₀-deuterated retinoids” is “completely proper” because no reasonable expectation of success is required for inherent properties of an obvious combination. Reply 8–9; *see also id.* at 17 (asserting that “no [reasonable expectation of success] is required for the natural result” of the “otherwise obvious” substitution of “C₂₀-deuterated vitamin A equivalents into existing [macular degeneration]-treatment regimens”); Tr. 6:11–7:3 (suggesting that, because C₂₀-deuterated vitamin A analogs were known in the art, nothing more is needed to show obviousness of the claims if “a person of skill in the art would understand that there would be no decline in function” by substituting vitamin A analog with its deuterated counterpart”).

To the extent Petitioner is making an inherency argument, we decline

to consider it because it was not the basis offered in the Petition for combining Bergen and Ortho Pharma with a reasonable expectation of success, *see* Pet. 40–43, and Petitioner may not change its theory of the case from the one presented in the Petition during trial. *See Intelligent Bio-Systems*, 821 F.3d at 1369 (explaining that “[i]t is of the utmost importance that petitioners in the IPR proceedings adhere to the requirement that the initial petition identify ‘with particularity’ the ‘evidence that supports the grounds for the challenge to each claim’” and holding that “the Board did not err in refusing the reply brief as improper . . . because [Appellant] relied on an entirely new rationale to explain why one of skill in the art would have been motivated to combine” the asserted prior art); *Arctic Cat Inc. v. Polaris Industries, Inc.*, 795 Fed. Appx. 827, 833 (Fed. Cir. 2019) (holding that “the Board did not misapply the law by requiring [petitioner] to prove the facts that it alleged”). We also note that obviousness requires that an ordinarily skilled artisan would have been motivated to make a combination, not merely whether the combination could have been made. *Virtek*, 97 F.4th at 886–87.

c) Objective Indicia of Non-Obviousness

Although we have determined based on the record before us that Petitioner has not shown by a preponderance of the evidence that a person of ordinary skill in the art would have had reason to combine the asserted prior art combinations to arrive at the claimed inventions with a reasonable expectation of success, we also find that Patent Owner’s evidence of objective indicia of non-obviousness supports a determination that the challenged claims would not have been obvious over the asserted prior art.

Patent Owner asserts that “long-felt need, failure of others, unexpected results, and praise demonstrate non-obviousness.” PO Resp. 49. Patent Owner points to, among other things, Alkeus Pharmaceuticals, Inc.’s deuterated vitamin A (C₂₀-D₃-retinylacetate) compound, variously referred to as ALK-001 or gildeuretinol. *Id.* at 51–57. In particular, Patent Owner cites to evidence based on “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),” which it asserts practices various claims of the ’045 patent, including independent claims 1, 28, and 29. PO Resp. 51 (citing Ex. 2191 ¶¶ 8–12, 15–19, 30–49; Ex. 2192 ¶¶ 266–270, 274–275, 289–293; Exs. 2086–2102).

Petitioner argues that any secondary considerations lack a nexus to the claimed invention because they are attributable to prior art features and are also not commensurate in scope with the claims; that there were no long-felt, unmet need or failure of others; that any such need remain unmet by the claimed invention; that any skepticism relate to unclaimed features; that industry praise are at best anecdotal and do not support non-obviousness, and that Patent Owner failed to show unexpected results. Reply 18–25.

Having considered the parties’ arguments and evidence, we find that, in totality, Patent Owner’s objective indicia evidence supports our determination of non-obviousness.

(1) Nexus to the SAGA and TEASE trials

“For objective indicia of non-obviousness to be accorded substantial weight, its proponent must establish a nexus between the evidence and the

merits of the claimed invention.” *Lectrosonics Inc. v. Zaxcom Inc.*, IPR2018-01129, Paper 33, 32 (PTAB January 24, 2020) (precedential) (“Lextrosonics”). To show nexus, Patent Owner must show that the evidence presented is reasonably commensurable with the scope of the claims. *Id.* A patentee is entitled to a presumption of nexus when the asserted objective evidence is shown to be tied to a product that embodies and is coextensive with the claimed features, but even without a finding of presumption Patent Owner can prove nexus by “showing that the evidence of secondary considerations is the ‘direct result of the unique characteristics of the claimed invention.’” *Id.* at 33 (quoting *In re Huang*, 100 F.3d 135, 140 (Fed. Cir. 1996)).

We find that Patent Owner has shown sufficient nexus between the use of ALK-001 in the SAGA and TEASE trials and at least independent claims 1, 28, and 29. In particular, ALK-001 (C₂₀-D₃-retinyl acetate) is one of the compounds recited in these claims. Ex. 2192 ¶ 50. Geographic Atrophy (SAGA trial) and Stargardt’s disease (TEASE trials) are diseases of macular degeneration. *Id.* ¶¶ 51, 52. Dr. Del Priore further provided a claim chart comparing various claims of the ’045 patent, including claims 1, 28, and 29, with the conduct of the TEASE and SAGA clinical trials. *Id.* ¶¶ 267–269.

Petitioner argues that evidence relating to ALK-001 is not probative, because “[t]he patent admits ALK-001 stability against the 1,5-shift naturally results from C₂₀-deuteration . . . , a prior art feature,” and “[o]rally administering daily vitamin A . . . to [macular degeneration] patients also was in the prior art.” Reply 18. We are not persuaded because, although the

nexus must be to an aspect of the claim not already in the prior art, Patent Owner may show, as it does here, that “it is the claimed combination as a whole [i.e., the use of C₂₀-deuterated compound to retard lipofuscin accumulation or treat macular degeneration] that serves as a nexus for the objective evidence.” *Lectrosonics*, 33.

Petitioner argues that Patent Owner’s “secondary considerations are not commensurate in scope with its claims” because none of the claims is directed to “the specific and undisclosed formulation” or protocol employed in the relied-upon clinical studies, and “[m]ost claims are not directed to Stargardt or ABCR-linked disease.” Reply 18–19.

We are not persuaded. Patent Owner may show that objective indicia evidence is commensurate with the scope of the claims by providing “an adequate basis to support the conclusion that other embodiments falling within the claim will behave in the same manner” as the embodiment discussed in the evidence. *In re Kao*, 639 F.3d 1057, 1068 (Fed. Cir. 2011).

In this case, we find Patent Owner has provided such a basis by relying on Dr. Del Priore’s testimony to argue that “[t]he demonstrated efficacy of ALK-001 in Stargardt’s [disease] 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,” and that “[t]his is confirmed by the efficacy of ALK-001 in SAGA for patients with geographic atrophy, an advanced form of dry AMD.” PO Resp. 52 (citing Ex. 2192 ¶¶ 103, 278–280, 294). Although Petitioner cites to Dr. Del Priore’s testimony to argue that excipient can have an effect on, e.g., absorption via the gut (Reply 18–19 (citing Ex. 1069,

271:6–273:24)), we do not find Dr. Del Priore’s testimony as suggesting that the effects of ALK-001 shown in the TEASE and SAGA trials depend on the use of specific excipients.

Finally, Petitioner argues that, because Patent Owner improperly withheld details of its clinical trials during discovery, no weight should be given to the studies. Reply 19. Although we encourage the parties to resolve discovery disputes without intervention from the Board, we also decline to exclude relevant evidence solely on the ground that additional evidence was requested but not produced, if the party seeking exclusion did not raise the issue with the Board in the first instance.

(2) Praise and Skepticism

Patent Owner argues that “there were concerns that administering deuterated vitamin A would not be effective” because “there [were] very few reports of deuterated derivatives being used as bona fide drug treatments.” PO Resp. 53 (citing Ex. 2192 ¶¶ 300–303; Ex. 2180, 14; Ex. 2179, 3; Ex. 2161, 9). Patent Owner argues that ALK-001 overcame this skepticism as evidenced by FDA’s Breakthrough Therapy Designation. *Id.* Patent Owner further cites to “praise from patients, families, and ophthalmologist.” *Id.* at 54 (citing Ex. 2183, Ex. 2149). Finally, Patent Owner cites to e-mail communications from Dr. Guengerich in 2010, who in his capacity as an editor at the Journal of Biochemistry provided reviewers’ comments to the inventor, Dr. Washington, on Dr. Washington’s “publications describ[ing] his invention.” PO Resp. 54.

Petitioner argues that the expressed skepticism lacked nexus to the claims, because they “related to *humans* maintaining the ‘tight dietary

control [that was] required to achieve these results in mice,”” whereas “[t]he patent lacks any claims regarding dietary control or humans,” and “all TEASE studies excluded patients taking vitamin A or beta-carotene.” Reply 23 (citing Ex. 1079, 133:16–135:7; Ex. 2098; Ex. 2099; Ex. 1070, 59:22–66:6). Petitioner argues that the “skepticism” allegedly evidenced by difficulty in obtaining venture capital funding “similarly address unclaimed features” and are undermined by other public statements by Alkeus. *Id.* at 24. Petitioner argues that there was no skepticism expressed about “the natural results of C₂₀-deuteration.” *Id.* at 24.

We agree that Patent Owner has not sufficiently shown nexus with respect to its evidence of skepticism. In particular, the evidence of skepticism generally relates to whether efficacy of C₂₀-deuterated vitamin A required “complete replacement of natural vitamin A with a C₂₀-D₃ analog.” Ex. 2161, el7; *see also* Ex. 2180, 14. However, the claims do not exclude embodiments where natural vitamin A is completely replaced with C₂₀-deuterated vitamin A. Similarly, evidence of difficulty in marketing the invention to biotech companies and venture capital — i.e., the response of “[t]oo early, too risky; come back with human data” — is insufficiently tied to the claims. Ex. 2179, 18.

Nevertheless, we find that the evidence of praise cited by Patent Owner supports a determination of non-obviousness.

First, Petitioner does not dispute the nexus between the claimed invention and Dr. Washington’s papers, respectively entitled “Deuterium enrichment of vitamin a at the C₂₀ position prevents the formation of detrimental vitamin a dimers in wild-type rodents” and “Prevention of

lipofuscin deposition in a mouse model of stargardt disease.” Exs. 2056, 2057. Patent Owner’s evidence shows that a reviewer of the first paper described it as “*innovative*,” and a reviewer of the second paper stated that there is “great interest” in Stargardt’s disease, which is of “significant clinical importance,” and that “[t]he use of a C20-D3-vitamin A is quite *novel* and interesting.” Ex. 2056, 2; Ex. 2057, 2 (emphasis added).

Although we agree with Petitioner that journal reviewer comments are not to be taken as patentability analyses, Pet. 25, such praise still serves as objective indicators of non-obviousness.

Likewise, although we do not put much if any weight on Patent Owner’s own press releases (*see, e.g.*, Ex. 2092) for purposes of evaluating “praise,” *In re Cree, Inc.*, 818 F.3d 694, 702, we find FDA’s Breakthrough Designation with respect to use of ALK-001 in treating Stargardt’s disease, and comments from FDA Patient Listening Session Summaries, to be probative and supportive of a determination of non-obviousness. *See, e.g.*, Ex. 2149, 4 (describing ALK-001 as having been granted breakthrough therapy designation by the FDA), 6 (under “Key Points presented by speakers” stating that “[a]s of June 2022, one potential treatment, ALK-001, has shown positive efficacy”).

In this regard, we acknowledge Petitioner’s arguments that FDA’s breakthrough and orphan designations “reflect *a desire* for successful results rather than a conclusion they were already obtained.” Pet. 24 (citing Ex. 2107, 2). We also acknowledge Petitioner’s argument that “hopeful patient anecdotes” do not suffice to show industry recognition or praise.

Nevertheless, we are not persuaded that only FDA approval may be probative of non-obviousness. *See, e.g., Sun Pharm. Indus., Inc. v. Incyte Corp.*, 2023 WL 5370639, *6 (Fed. Cir. 2023) (agreeing that FDA designation of a drug as “Breakthrough Therapy” is probative of non-obviousness but holding Board reasonably found that the drug had not met long-felt need where Patent Owner “expressly framed its objective indicia argument as . . . ‘satisf[ying] the long-felt need for an *FDA-approved*, evidence-based . . . treatment’; *see also* Ex. 2192 ¶ 54 (explaining that FDA’s Breakthrough Therapy designations are given to drugs “that treat a serious or life-threatening condition where ‘preliminary clinical evidence indicates that the drug may demonstrate substantial improvement over available therapy on a clinically significant endpoint(s)’”). Similarly, Petitioner does not cite to any authority that patient anecdotes cannot be probative of non-obviousness.

(3) *Long-Felt Need*

Patent Owner argues that, as of 2007, there was a need for “treatments to slow the progression of macular degeneration resulting from lipofuscin accumulation . . . *without* inducing visual impairment such as night blindness or impaired dark adaptation,” which was long-recognized, substantial, and unmet despite “intense research.” PO Resp. 49–50.

Petitioner argues that there were no unmet need or failure of others. Reply 19–20, 22. In particular, with respect to slowing lipofuscin formation, Petitioner argues that “visual-cycle inhibition successfully reduced lipofuscin formation,” only with “unnecessary” side-effects; that “prior art ‘reflected optimism about slowing [macular degeneration] progression’; that

Patent Owner “identifies no technical obstacle to using deuterated-vitamin A to retard lipofuscin formation,” which was validated by mechanistic studies leading to the critical date; that literature leading to the critical date called “specifically to retard the A2E-byproduct pathway . . . rather than induce blindness and serious side effects” and also evidenced “surging interest in deuterating known compounds.” Reply Br. 22 (citing, *e.g.*, Ex. 1080 ¶¶ 13, 30–36, 72, 73; Ex. 2074, 5–6, 11; Ex. 1069, 193:7–197:4).³⁰

We find that there is sufficient evidence to support Patent Owner’s position. For instance, as evidenced by Mata, A2E biosynthesis pathways have been proposed since at least as early as 2000. Ex. 1010, 7158, Fig. 5. However, Travis³¹ teaches that, as of 2007, the “[s]everal approaches [that] have been tested or proposed to slow accumulation of A2E . . . [a]ll have an effect on visual-cycle retinoids and ultimately limit the formation of [ATR].” Ex. 2003, 14. Travis further teaches that they were either impractical (*e.g.*, requiring treatment subjects to be in total darkness) or had side effects due to inhibition of the visual cycle such as varying degrees of delayed dark

³⁰ Petitioner asserts Patent Owner’s argument regarding “unmet need for an *oral* AMD treatment is not commensurate with the challenged claims,” and no technical difficulty prevented developing oral medication, as evidenced by prior art oral vitamin A administration to macular degeneration patients and other oral medications in development. Reply Br. 23. However, we do not read Patent Owner’s arguments and evidence regarding secondary considerations to be limited to oral AMD treatments. Sur-reply 19–20.

³¹ Gabriel H. Travis et al., *Disease Caused by Defects in the Visual Cycle: Retinoids as Potential Therapeutic Agents*, ANN. REV. PHARMACOLOGY & TOXICOLOGY 469 (2007) (Ex. 2003, “Travis”). When citing to Travis, we refer to the page numbers added by Patent Owner.

adaptation and, possibly, photoreceptor degeneration. *Id.* at 12–16; *see also* PO Resp. 49 (citing evidence). This evidence weighs in favor of non-obviousness “because it is reasonable to infer the need would not have persisted had the solution been obvious” as Petitioner claims. *Apple Inc. v. Samsung Electronics Co., Ltd.*, 839 F.3d 1034, 1056 (Fed. Cir. 2016).

Petitioner also cites to two FDA approved drugs for Geographic Atrophy, a form of macular degeneration, to argue that there were no long-felt, unmet need or failure of others. Reply 19–20; Ex. 1069, 218:8–10. We are not persuaded, because these drugs were approved in 2023, and the references cited by Petitioner in the Reply relating to these drugs were also dated several years after 2007, the effective filing date of the patent. *See* Ex. 1069, 232:18–234:20; Ex. 2171; Ex. 1066; *see also Procter & Gamble Co. v. Teva Pharms. USA, Inc.*, 566 F.3d 989, 998 (Fed. Cir. 2009) (looking to “filing date of the challenged invention to assess the presence of a long-felt and unmet need”).

Petitioner argues that, to the extent a long-felt need exists, Patent Owner has not shown that its invention met the need. Reply 20–22 (citing, *e.g.*, Ex. 2192 ¶¶ 282, 286). More particularly, Petitioner argues that “the SAGA trial was unable to report they met the prespecified primary endpoint,” and the TEASE trials were conducted using “inexperienced personnel” and problematic protocols. *Id.* at 20–21 (citing, *e.g.*, Ex. 1069, 237:7–239:5, 239:12–240:5, 267:1–268:7; Ex. 2179, 3; Exs. 1074–1078; Ex. 1079, 81:4–84:25, 87:7–94:16, 151:4–13, 181:7–204:2; Ex. 1087, 19). Petitioner argues that, although Patent Owner “presented brief interim-result abstracts, a full, peer-reviewed publication of the study never followed.” *Id.*

at 21 (citing Exs. 2086, 2087; Ex. 1079, 77:18–20, 117:20–23, 228:20–230:2).

However, as to the SAGA trial, Patent Owner has provided evidence that treatment with ALK-001 was “associated with slower growth of GA ([geographic atrophy]) lesions and improved visual acuity,” even if the trial did not meet the prespecified primary endpoint. Ex. 2094, 1; Sur-Reply 20–21. Likewise, Petitioner does not persuasively show that any alleged irregularity in the TEASE study protocol casts doubt on the reported outcome of the trial, i.e., that after two years “ALK-001 was shown to safely slow the growth of retinal atrophy . . . by 21%” with “no reports of night blindness or delayed dark adaptation.” Ex. 2192 ¶ 291 (citing Exs. 2088, 2089). Accordingly, we find that the totality of the evidence regarding long-felt need supports a finding of non-obviousness. *Ashland Oil, Inc. v. Delta Resins & Refractories, Inc.*, 776 F.2d 281, 306 (Fed. Cir. 1985) (explaining that objective indicia evidence “may in any given case be entitled to more or less weight, depending upon its nature and its relationship to the merits of the invention”).

(4) Conclusion

Accordingly, for the reasons discussed above, we find that objective indicia evidence, for instance at least with respect to praise and long-felt need, also supports a finding of non-obviousness.

d) Additional Patent Owner Arguments

Because we find the above issues to be dispositive that Petitioner has not shown, by a preponderance of evidence, that an ordinarily skilled artisan

would have had reasonable expectation of retarding lipofuscin accumulation or treating macular degeneration by administering deuterated vitamin A, and thus would not have had motivation to do so, and because we find the totality of the evidence of objective indicia to support non-obviousness, we do not address additional arguments from the Patent Owner and Petitioner's responses thereto.

3. Alleged Obviousness Over Ortho Pharma, Bergen, and Mata

Petitioner argues that claims 10–15, 18, 37–42, and 45 would have been obvious in view of Ortho Pharma, Bergen, and Mata. *See* Pet. 46–55. For this challenge, Petitioner relies on Mata as teaching the additional limitations of dependent claims 10–15, 18, 37–42, and 45 that “the patient in need has a specific ocular disorder,” but relies on the same rationale as in Ground I for the reason to combine Ortho Pharma and Bergen with a reasonable expectation of success. *Id.*

For the same reasons discussed above, we find that Petitioner has not adequately demonstrated that a person of ordinary skill in the art would have been motivated to combine Ortho Pharma, Bergen, and Mata to arrive at the methods of claims 10–15, 18, 37–42, 45, with a reasonable expectation of success. *See supra* Section II.D.2. Accordingly, we determine that Petitioner has not demonstrated by a preponderance of the evidence that claims 10–15, 18, 37–42, and 45 would have been unpatentable as obvious over the combination of Ortho Pharma, Bergen, and Mata.

4. Alleged Obviousness Over Ortho Pharma, Bergen, Mata, and Widder

Petitioner argues that claims 16, 17, 24, 27, 43, 44, 51, and 54 would have been obvious in view of Ortho Pharma, Bergen, Mata, and Widder. *See* Pet. 55–65. For this challenge, Petitioner relies on Widder as teaching the additional limitations of dependent claims 16, 17, 24, 27, 43, 44, 51, and 54, in particular treating retinitis pigmentosa, co-administering negatively-charged phospholipids, and administering treatment directly to the eye, but relies on the same rationale as in Ground I for the reason to combine Ortho Pharma and Bergen with a reasonable expectation of success. *Id.*

For the same reasons discussed above, we find that Petitioner has not adequately demonstrated that a person of ordinary skill in the art would have been motivated to combine Ortho Pharma, Bergen, Mata, and Widder to arrive at the methods of claims 16, 17, 24, 27, 43, 44, 51, and 54, with a reasonable expectation of success. *See supra* Section II.D.2. Accordingly, we determine that Petitioner has not demonstrated by a preponderance of the evidence that claims 16, 17, 24, 27, 43, 44, 51, and 54 would have been unpatentable as obvious over the combination of Ortho Pharma, Bergen, Mata, and Widder.

III. PETITIONER’S MOTION TO EXCLUDE

Petitioner moved to exclude Exhibits 2001, 2002, 2004, 2005, 2007, 2010–2013, 2015, 2020, 2021, 2024, 2026, 2036, 2037, and 2077, and portions of Exhibit 2192 (Del Priore Declaration), in particular Dr. Del Priore’s proffered opinions regarding enzyme reaction kinetics and “all testimony relying directly or indirectly upon that subject matter,” including

paragraphs 62, 109, 175, 179, 210–11, 216, and 221.³² Because we do not rely in our analysis on these exhibits or the portions of the Del Priore Declaration at issue in a manner adverse to Petitioner, we dismiss the Motion to Exclude as moot.

IV. CONCLUSION

In summary:

Claim(s)	35 U.S.C. §	Reference(s)/ Basis	Claim(s) Shown Unpatentable	Claim(s) Not Shown Unpatentable
1–9, 19–23, 25, 26, 28–36, 46–50, 52, 53	103(a)	Ortho Pharma, Bergen		1–9, 19–23, 25, 26, 28–36, 46–50, 52, 53
10–15, 18, 37–42, 45	103(a)	Ortho Pharma, Bergen, Mata		10–15, 18, 37–42, 45
16, 17, 24, 27, 43, 44, 51, 54	103(a)	Ortho Pharma, Bergen, Mata, Widder		16, 17, 24, 27, 43, 44, 51, 54
Overall Outcome				1–54

V. ORDER

In consideration of the foregoing, it is hereby:

ORDERED that Petitioner has not demonstrated by a preponderance of the evidence that claims 1–54 of U.S. Patent No. RE47,045 E are unpatentable; and

³² Although Petitioner originally included Exhibits 2018, 2025, and 2033 in the Motion to Exclude, Petitioner notes in the Reply to Patent Owner’s Opposition that they were mistakenly included. Mot. Reply 2–3.

FURTHER ORDERED that, because this is a final written decision, parties to this proceeding seeking judicial review of our Decision must comply with the notice and service requirements of 37 C.F.R. § 90.2.

IPR2024-00313
Patent RE47,045 E

FOR PETITIONER:

Jad A. Mills
Michael T. Rosato
Matthew Bresnahan
WILSON SONSINI GOODRICH & ROSATI
jmills@wsgr.com
mrosato@wsgr.com
mbresnahan@wsgr.com

FOR PATENT OWNER:

Mark J. Feldstein
Joshua L. Goldberg
Drew D. Christie
Matthew Hays Everhart
William Neer
FINNEGAN, HENDERSON, FARABOW, GARRETT & DUNNER, LLP
mark.feldstein@finnegan.com
joshua.goldberg@finnegan.com
drew.christie@finnegan.com
matthew.everhart@finnegan.com
william.neer@finnegan.com

Eliot D. Williams
Paul A. Ragusa
Carolyn Pirraglia
BAKER BOTTS L.L.P.
eliot.williams@bakerbotts.com
paul.ragusa@bakerbotts.com
carolyn.pirraglia@bakerbotts.com