

REDACTED PUBLIC VERSION

Filed: December 23, 2024

UNITED STATES PATENT AND TRADEMARK OFFICE

BEFORE THE PATENT TRIAL AND APPEAL BOARD

GENE COMPANY PTY LTD,
Petitioner,

v.

THE TRUSTEES OF COLUMBIA UNIVERSITY
IN THE CITY OF NEW YORK,
Patent Owner.

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

PETITIONER'S REPLY
U.S. PATENT NO. RE47,045

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I. INTRODUCTION

The POR contradicts the record and is filled with mischaracterizations. PO argues the art teaches away from administering vitamin A to macular degeneration (MD) patients in favor of using blindness-inducing medications, but PO's clinician testified the opposite was true. PO's remaining arguments fare no better. PO mischaracterizes Dr. Guengerich's testimony and asserts false and erroneous arguments against reasonable expectation of success (REOS). But Dr. Guengerich comprehensively rebutted these false arguments, and confirms the petition's reasoning and articulated REOS.

Next, PO employs the same misleading tactics in its secondary-considerations case, arguing prior-art therapies failed, while its clinical trials succeeded, although its expert testified the opposite was true. PO's alleged "success" should be accorded no weight because no meaningful evidence shows success. PO bore the burden of production but produced only its own cursory interim press releases and meeting abstracts rather than peer-reviewed study publications. PO also obstructed discovery into the studies' methodologies, hiding their inadequacies. All that remains are self-serving documents from an interested party without detail or underlying data, which should not be credited.

II. OBVIOUSNESS

A. PO's Teaching-Away Argument Is Meritless

PO primarily argues the prior art taught away from administering vitamin A to MD patients. POR 16-24, 60-62. Yet, what PO labels teaching away is an improper piecemeal attack on individual references, not evidence that a POSA would have been actively discouraged from the proposed combination. *In re Keller*, 642 F.2d 413, 426 (CCPA 1981). The petition proposed substituting *C₂₀-deuterated* vitamin A for the prior-art vitamin A administered to MD patients. *E.g.*, Pet. 40-43. PO identifies no teaching away from this proposed combination.

PO's teaching-away argument also is factually incorrect. Building on long-held suggestions and "common perceptions," the AREDS study successfully prevented age-related MD (AMD) progression in high-risk patients. EX1080, ¶76; EX1069, 97:9-99:14, 106:10-109:19. Ortho Pharma (EX1008) thus reflects common practice to administer 15 mg of beta-carotene *plus* the recommended-daily-allowance (RDA) ~1 mg of vitamin A to high-risk AMD patients to slow disease progression. EX1080, ¶¶75-77; EX1069, 116:21-119:20, 68:8-70:17, 71:6-74:15; EX1022, 7-8; EX1065 (CENTRUM ingredients), EX1069, 62:1-63:6, 142:11-25, 144:11-17 (beta-carotene is claimed). *PO*'s clinician followed this recommendation. EX1080, ¶75; EX1069, 87:1-88:22, 90:6-92:19, 104:13-105:2; EX1069, 57:12-60:23 (30-50% take multi-vitamin).

Additionally, vitamin A was safely administered to treat retinitis pigmentosa patients, Sorsby's fundus patients, and even Stargardt patients, e.g., at doses up to ~14 times the RDA. EX1080, ¶¶76; EX1069, 123:2-129:22, 131:10-132:6, 164:15-167:14. The Ortho Pharma doses higher than AREDS protocol correspond to prior-art practices for treating other claimed lipofuscin-associated diseases. EX1069, 120:12-121:2, 137:7-139:4.

PO argues administering vitamin A would increase lipofuscin formation by increasing serum concentrations. But serum vitamin A concentrations were "highly regulated," EX1080, ¶¶74, 79; EX1069, 143:4-12; EX2103, 173:8-177:20; EX1002, ¶¶70-72, 74-75. AREDS (EX1022, 7-8) reported no significant vitamin A serum-concentration increases *after years of treatment*. EX1080, ¶77; EX1069, 63:10-68:7, 88:23-90:5. And PO provides no evidence these vitamin A serum levels were associated with increased lipofuscin formation.

Moreover, ABCR-linked lipofuscin formation was tied to an imbalance in all-*trans*-retinal concentration in a very specific locus in the eye, rather than in serum concentrations. EX1080, ¶¶65-66, 69-70; EX2052, ¶¶89 n.15, 94 n.19, 100 n.21, 103 n.22; EX1034, 1; EX2019, 6; EX1070, 106:1-107:20, 141:16-142:6, 152:21-153:9, 156:3-158:2; EX1070, 111:8-21 ("excess" ATR accumulation in the disc interior); *see also* EX1080, ¶¶40, 48-49 (RmP deficiency). Replacing vitamin A with C₂₀-deuterated vitamin A was reasonably expected to inhibit the 1,5-shift

that was required for lipofuscin formation, while preserving the sight-essential function of the visual cycle. EX1080, ¶¶74, 79; EX1002, ¶¶70-72, 74-75 (dietary sources less absorbable). PO's concession that supplemented vitamin A would reach the eye thus confirms the claims' obviousness.

PO's argument that a POSA must induce vitamin A deficiency to treat Stargardt patients also fails. Deficiency and other visual cycle-inhibition experiments demonstrated A2E/lipofuscin was an unnecessary byproduct of the sight-essential visual cycle. EX1080, ¶¶30, 35, 65-67; EX2052, ¶56; EX2058, 1; EX2074, 4-6; EX1069, 181:9-182:16 (minor byproduct), 192:20-25 (side reaction); EX1002, ¶¶59-69. PO's clinician agreed inhibiting the visual cycle (by withholding vitamin A or using cycle inhibitors) predictably resulted in serious disease and blindness. EX1080, ¶¶33-34; EX1069, 216:20-217:2 ("photoreceptor cell death and loss of vision"), 217:12-16 ("delayed dark adaptation and night blindness"); 135:8-136:16 ("cause night blindness and eventual death of photoreceptors"), 29:18-32:16 (risks "irreversible" damage), 57:1-9 (vitamin A is essential to vision); EX1069, 214:13-215:11 (isotretinoin "too toxic for long-term administration in humans"; side effects "would preclude long-term therapy"), 210:2-211:8 (doses necessary "would be toxic"), 203:15-204:21 (decreasing vitamin A was "impractical as a treatment or therapy" to inhibit A2E/lipofuscin accumulation), 46:17-24 ("you need the integrity of this visual pathway....If you

interfere at any step...[t]here is a variety of things that can happen, none of which are good.”), 52:15-53:6 (inhibiting 11-*cis*-RDH causes vision loss), 55:2-14 (inhibiting RPE65 causes disease), 49:19-50:9 (severe vision loss); EX1004, ¶¶76-79; EX1002, ¶¶65, 67-68, 71, 76 (inhibit A2E/lipofuscin without inhibiting visual cycle). The prior art rejected PO’s false dichotomy—blind the patient by withholding vitamin A or inhibiting the visual cycle, or let the patient go blind over time. EX1080, ¶¶28-32, 35; EX2019, 7 (expressly suggesting embracing “yet other novel approaches to therapy” based on the “[i]mproved understanding of the mode of genesis of A2E” rather than inhibit the visual cycle); EX1069, 203:6-14 (POSA aware that recent efforts for treating AMD and Stargardt “have centered on targeting A2E formation”), 183:14-20 (inhibiting A2E-byproduct pathway “should not impact the vision cycle”). The Board should reject it too. EX1080, ¶¶79, 28-29.

B. PO’s Attacks On Motivation Fail

i. PO Mischaracterizes “Rate-Limiting” Evidence

PO argues incorrectly that Dr. Guengerich “abandoned” and “disavowed” the petition’s “rate-limiting” argument because he testified a POSA would have recognized the 1,5-shift likely was “a” rate-limiting step even if it was not “the” only step that could do so. POR 24-29, 37, 57-58. EX1080, ¶¶16-18; EX2103, 55:12-56:10 (“So you may have *more than one rate-limiting step* [i]n the

process.”),¹ 56:24-57:14, 57:22-23, 64:1-14, 65:3-7. But Dr. Guengerich repeatedly explained C₂₀-deuteration likely *would* inhibit the A2E-biosynthetic pathway.

EX1080, ¶19; EX2103, 58:2-12 (“if you inhibit [the 1,5-sigmatropic rearrangement], *you will block the accumulation of the APE* intermediate, and then you’ll actually have less material to go on to the subsequent products, regardless of how slow or fast they are.”), 63:19-25 (“it doesn’t matter if the subsequent steps are slow...*attenuate the first one. Then you will actually lead to less of a final product.*”), 89:13-21 (“you can slow down the overall reaction”), 65:8-21 (“the 1,5-sigmatropic rearrangement presents what...a POSA would consider *the easiest route to inhibition*”); 56:13-23 (“[T]he first step is the 1,5-sigmatropic rearrangement”). He explained the 1,5-shift was slow enough under physiological conditions to be rate-limiting, because “forced” conditions were required to expedite. EX1080, ¶20; EX2103, 121:6-123:12.

PO’s entire argument hinges on arguing the 1,5-shift must be *the* slowest step to be a rate-limiting step. However, PO is wrong. EX1080, ¶¶21-24. Even Dr. Prestwich conceded that multiple steps can be rate-limiting. EX1080, ¶21; EX2052, ¶119 (preventing A2E/lipofuscin “requires identification of rate-limiting *steps*”). Reducing the 1,5-shift reduces reactant concentration for subsequent

¹ All bold-italic emphases added.

reactions, which Dr. Prestwich agrees affects their rates. EX1080, ¶¶22-24; EX2052, ¶¶104, 110, 184, 198. Indeed, 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. EX1080, ¶¶23; EX2052, ¶¶50, 56. Dr. Prestwich identified various visual-cycle steps as rate-limiting. EX2052, ¶¶76, 84 (reduction of ATR), 85 (RPE65). He proposes inhibiting still other enzymes that he does not claim are rate-limiting. EX2052, ¶¶116 (11-*cis*-RDH). PO's argument that the 1,5-shift must be *the one and only* rate-limiting step should be rejected.

ii. PO's Rate-Calculation Arguments Fail

PO argues it would be difficult to calculate *a priori* the "slowest" reaction rather than perform kinetic isotope effect (KIE) studies to confirm rate-limiting steps. POR 29-32. But calculating rates was not required. There is no absolute requirement that there be only a single, slowest rate-limiting step. EX1080, ¶¶21-25. Moreover, Mata presented information sufficient to reasonably expect the 1,5-shift was *a* rate-limiting step that was desirable to inhibit. (EX1080, ¶¶25-27, 38-40).

Indeed, Dr. Guengerich testified the prior art disclosed the reaction was so slow under physiological conditions it had to be forced. EX1080, ¶¶52-53; EX2103, 120:6-19 ("a slow reaction"; not very efficient), 123:2-6 (conditions

“used to force the reaction”). After Roth and Itou, PO submitted Doering 2006 (EX2025)—which corroborated both the 1,5-sigmatropic rearrangement’s specific slowness and its large expected KIE. EX1080, ¶52 (~12-16); EX2103, 124:8-21 (Roth and subsequent prior art recognized cleavage of the referenced carbon-hydrogen bond was slow under physiological conditions); EX2103, 61:24-62:2, 73:6-74:4, 75:5-6 (Doering); EX2025, Abstract. PO’s argument that “no art suggest[ed]” the 1,5-shift was likely rate-limiting is simply wrong. POR 33-34.

PO’s improper-hindsight argument (POR 34-35) also fails. Dr. Guengerich testified repeatedly that *Mata* and *Fishkin* provided good reason to inhibit the 1,5-shift *before* the ’045 patent, by disclosing the 1,5-sigmatropic rearrangement is just upstream of the path divergence between A2E and ATR-dimer, but downstream of ATR formation, to inhibit undesirable lipofuscin formation without disrupting the visual cycle. EX1002 ¶¶84-85, 93-98, 184. Dr. Guengerich did *not* rely on the challenged patent for hindsight. EX2103, 39:9-43:3 (“I’m not relying on it...it just says that it’s in the patent, but it is also in the open literature...that was published well before the patent”); EX1080, ¶38. Noting patentee admissions about skill level and properties inherent to C₂₀-deuterated retinoids (Pet. 45-46; EX1002 ¶266) is also completely proper. *Qualcomm Inc. v. Apple Inc.*, 24 F.4th 1367, 1376 (Fed. Cir. 2022) (recognizing patentee admissions about skill level is not improper hindsight); *Cytiva BioProcess R&D AB v. JSR Corp.*, 2024 U.S. App. LEXIS

30503, at *21 (Fed. Cir. Dec. 4, 2024) (no REOS required for inherent property of obvious combination (citing *Hospira, Inc. v. Fresenius Kabi USA, LLC*, 946 F.3d 1322, 1332 (Fed. Cir. 2020))).

PO mischaracterizes Dr. Guengerich as stating C-H bond breaking generally was viewed as relatively rapid until 2012. POR 34. The cited statements relate to a specific C-H bond broken in the cytochrome P450 enzyme catalytic cycle. EX1080, ¶46; EX2083, 1; EX2009, 199:4-201:5. When PO's crop-quotes are restored, Dr. Guengerich's 2005 publication states his results (published as early as 1988) teach C-H bond-breaking was not relatively rapid. EX1080, ¶46; EX2083, 1 & refs. 40-45. PO's mischaracterization of Dr. Guengerich's statements should be rejected.

PO argues it was obvious to reduce lipofuscin by inhibiting the visual cycle to slow bimolecular condensation of NRPE with a second molecule of all-*trans*-retinal. POR 32-33. But PO's argument ***underscores*** the importance of inhibiting the 1,5-shift, which directly reduces the limiting-reactant (activated NRPE) concentration in the bimolecular condensation. EX1080, ¶¶41-42; EX2052, ¶¶197-204 (reaction required "sufficient concentrations of each molecule"). Moreover, regardless of the A2PE-to-A2E conversion rate or the RPE cell-phagocytosis rate (POR 33 n.7), inhibiting the 1,5-shift would reduce the amount of A2PE and the

resulting A2E concentration. EX1080, ¶¶43-45. PO's other "likely rate-limiting" steps do not undermine motivation or REOS. EX1080, ¶¶41-45.

iii. PO Ignores Specific Reasons to Inhibit 1,5-Shift

1. Specific Suggestions in Mata/Fishkin/Kim

PO argues the petition failed to establish any specific motivation to inhibit the 1,5-shift because Mata's direction to inhibit "one or more steps in the A2E synthetic pathway" applies to any of the "one or more" steps" upstream of A2E and downstream of the visual cycle. POR 35-37. But PO is wrong again. EX1080, ¶¶38-40. Inhibiting the 1,5-shift stood out to a POSA reviewing Mata and Fishkin because it is upstream of the branch point forming *both* A2E and ATR-dimer, and also downstream of the visual cycle (to avoid unnecessary side effects). EX1002 ¶¶84-85, 93-98, 184. The 1,5-shift is thus the first and best point for intervention in the byproduct pathway and was expected to provide recognized benefits. EX1080, ¶¶38-40; *see also* EX1080, ¶19; EX2103, 65:8-21 ("the easiest route to inhibition"); 89:13-21 (the "first step" after the initial condensation of ATR and PE); EX2103, 58:2-12 ("if you inhibit [the 1,5-sigmatropic rearrangement], you will block the accumulation"), 63:19-25 ("it doesn't matter if the subsequent steps are slow").

PO also argues "pharmacological inhibition" categorically excludes deuterium substitution. POR 37. But PO misinterprets Mata, which targeted

“precursors of A2E,” not proteins, for inhibition. EX1080, ¶¶37, 65; EX2074, 4.

Limiting inhibition to enzyme inhibitors is simply another of PO’s misguided arguments that a POSA was required to inhibit the visual cycle (dominated by enzymatic steps) rather than the straightforward A2E-byproduct pathway disclosed in Mata. EX1080, ¶¶32-37, 63; EX1011, 7091 (“random/nonenzyme-mediated reactions”). PO’s proposal to inhibit the visual cycle is a surefire way to “get disease” (EX1069, 45:17-25), and should be rejected.

2. PO’s Attacks on Roth and Itou Fail

PO argues the large KIE reported in Roth and Itou should be ignored. POR 40-44. PO is wrong again. EX1080, ¶¶51-64.

First, PO argues Roth and Itou are irrelevant because, allegedly, Mata was incorrect about 1,5-sigmatropic rearrangement. POR 40-42. PO argues the reaction is a fast, acid-base tautomerization, like the one shown in Mowery and Verdegem. *Id.*; EX1080, ¶¶55-56. But the harsh, alkaline conditions used in Mowery and Verdegem (on other compounds) are indisputably not the relevant *physiological* conditions. EX1080, ¶¶58, 61-62; EX1070, 159:16-161:13 (sodium hydride is non-endogenous, caustic, and combustible; not physiological conditions); EX2052, ¶¶94-96 (A2PE formation from ATR and PE occurs physiologically at “neutral pH”). Just like Roth and Itou, Mowery and Verdegem had to apply “extreme

conditions” to drive a reaction that was indisputably “slow” under physiological conditions. EX1080, ¶¶58-59, 63.

Even if Dr. Prestwich were correct that *A2E* can be formed via enzyme-catalyzed, acid-base-induced C₂₀-deprotonation, this does not support PO’s argument that no significant KIE would be expected from C₂₀-deuteration. EX1080, ¶¶55-56, 59. To the contrary, Dr. Prestwich’s proposed alternative reaction mechanism also was “prone” to a strong KIE. EX1080, ¶¶59-60, 63-64. PO’s proposed deviation from Mata’s description of the reaction cannot undermine motivation or REOS. *Intelligent Bio-Systems v. Illumina Cambridge*, 821 F.3d 1359, 1367 (Fed. Cir. 2016) (no guarantee required, just reasonable expectation); *Pfizer, Inc. v. Apotex, Inc.*, 480 F.3d 1348, 1364 (Fed. Cir. 2007) (“need only be reasonable, not absolute”).

Second, PO argues Roth’s “large KIE is property of the highly symmetric cis-pentadiene hydrocarbon,” but NRPE would lack a large KIE because it was an “asymmetric” molecule. POR 42-43. But PO’s argument conflates *structural asymmetry* of a molecule with a non-symmetrical *transition state*. EX1080, ¶57. As Dr. Guengerich testifies, “Mata’s identification of the NRPE reaction as a [1,5]-sigmatropic rearrangement” gave a POSA good reason to expect a transition state prone to a strong KIE. *Id.*

Finally, PO argues Roth's reported KIE does not guarantee another step in A2E synthesis might not "mask" that effect somewhat. POR 43-44. As Dr. Guengerich explains, however, PO'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. EX1080, ¶54. KIE studies were so routine and straightforward, PO's concerns would not dissuade a POSA from measuring the KIE that naturally results from this favorable substitution. EX1080, ¶¶54-55, 10-11, 26-27; EX2052, ¶¶129 n.33 ("elucidating metabolic and biosynthetic pathways"), 131-133 ("intrinsic" KIE), 187 n.47 ("[i]n practice," a POSA would measure observed KIE rather than agonize over calculations).

PO's speculative masking arguments also require exaggerated biological complexity that ignores the straightforward task of inhibiting the slow but undesirable NPPE modification in the disc interior. EX1080, ¶¶65-71. The prior art suggested specifically inhibiting the A2E-byproduct pathway rather than the visual cycle, so unresolved visual-cycle questions are irrelevant. EX1080, ¶¶65, 67. PO would distract from inhibiting the 1,5-shift (known to unleash bimolecular condensation) by pointing to steps known to occur *after* irreversible A2PE-H₂ formation. EX1080, ¶¶66, 68-71. None of PO's arguments "call into question the ability of C₂₀-deuteration to inhibit A2E formation." *Id.*

C. PO Disregards the POSA's Practical KIE Knowledge

PO redefines the POSA to ignore KIE. POR 6-8. But practical knowledge about deuterium KIE was in the POSA's toolkit. EX1002, ¶¶53-55, 99-123; EX1080, ¶¶4, 9-11, 14. Even Dr. Prestwich seems to agree. EX1070, 37:3-10 (defining the relevant field to include biochemistry); EX2052, ¶¶129-130 ("As of September 2007, the deuterium kinetic isotope effect was recognized as a versatile tool"), 139 ("improve drugs by slowing or redirecting their enzymatic metabolism."), 152 ("alter the properties of known pharmaceuticals"). PO's self-serving and unsupported redefinition of the POSA to exclude KIE should be rejected.

i. C₂₀-Deuteration Is A Classic Application of DKIE

PO argues using C₂₀-deuteration to slow the 1,5-shift "is fundamentally different" than increasing pharmacologic-action duration or reducing undesirable metabolic action. POR 38-40. But this is incorrect. Using deuterium to slow the 1,5-shift indisputably was within the POSA's technical ability, and C₂₀-deuteration was a classic application of deuterium to improve a known active (vitamin A). EX1080, ¶¶47-50. Prior-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. EX1080, ¶48. A POSA would have expected this approach to "preserve the vitamin A nutrient (analogous to

stabilizing the desired drug for a prolonged, desired effect) while also reducing production of the undesirable, toxic byproduct (analogous to metabolic switching).” EX1080, ¶¶48-50. C₂₀-deuteration thus “fits well within the established paradigm.” EX1080, ¶¶48, 50.

ii. Recognized, Recent Interest in Deuterium Substitution

PO argues no significant interest in deuterium substitution existed before the critical date and deuterium substitution was “speculative.” POR 39. These are incorrect. EX1002, ¶¶99-115 (deuterium KIE substitution well-accepted). PO’s arguments ignore evidence *PO submitted* detailing years of successful experience using targeted deuteration to improve safety and/or efficacy while maintaining selectivity and potency. EX1080, ¶12; EX2008, 25-27, 31. PO’s evidence also details significant interest in deuterium substitution and proliferating patent filings for deuterium-substituted compounds. EX1080, ¶13; EX2008, 31-41. PO minimizes and ignores the rising focus on deuterium substitution at the critical date.

D. PO’s Attacks On Reasonable Expectation Fail

PO argues no REOS existed for identifying the “effective amount” of C₂₀-deuterated vitamin A to retard lipofuscin, treat MD, or slow A2E in vitro by about 7 times. POR 44-46, 58-59, 61. But the claimed effective amount is as low as 0.1 mg. EX1001, claims 19, 46. Again, PO ignores that the prior art disclosed

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dosages and ranges (e.g., 1-15 mg or more) for vitamin A and pro-vitamin A carotenoids that were being administered to treat MD. *See* Section II.A above; Pet. 8-9, 22, 33, 37-39, 43-45. PO's claimed "effective amount" range (0.1-90 mg) clearly encompasses the prior art. *Titanium Metals Corp. v. Banner*, 778 F.2d 775, 782 (Fed. Cir. 1985) (prior disclosure of point anticipates the range); *E.I. du Pont de Nemours & Co. v. Synvina C.V.*, 904 F.3d 996, 1008 (Fed. Cir. 2018) (overlapping prior art range renders claim *prima facie* obvious). Moreover, the patent admits efficacy naturally results from C₂₀-deuterium substitution. *E.g.*, Pet. 35-36 (citing EX1001). PO also does not challenge the patent's admissions that dosing, formulation, and administration means (including oral) all were routine and within the POSA's skill. *E.g.*, Pet., 29, 45-46 (citing EX1001). PO cannot now repudiate its admissions to challenge REOS.

PO wants to distinguish its claims from prior-art "nutritional supplements" (POR 45-46), but they encompass administering the prior-art compound in a "nutraceutical composition" or as a "vitamin supplement." *E.g.*, Pet. 24-25, 32-33; EX1001, claims 3, 31. PO's speculation that administering vitamin A "could lead to more lipofuscin formation" (POR 46-47) is unpersuasive. *See* Section II.A above. PO's failure-of-others arguments also are unpersuasive. *See* Section II.E.ii below.

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PO's "ancillary" argument (POR 47-48) ignores the petition's REOS analysis. *E.g.*, Pet. 35-37, 42-46; EX1002, ¶¶60 (maintain desired functionality), 99-102 & 107-109 (reduce lipofuscin formation 2-10x), 121-122 (large KIE expected to slow A2E formation), 178, 260-263, 269, 352 (similar), 240-244 (natural result); EX1004, ¶¶82-84 (AMD treated with pro-vitamin A), 85 (claimed diseases treated with vitamin A), 142-146 (expected to reduce lipofuscin formation). C₂₀-deuteration was reasonably expected to inhibit the 1,5-shift, and this is true even if PO's postulation is correct that the 1,5-shift was unleashed endogenously via acid-base removal of a C-20 hydrogen. EX1080, ¶¶36, 58-64 (acid-base-catalysis invoked by Dr. Prestwich "prone to strong KIEs").

Because 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 MD, including dry AMD and Stargardt. *E.g.*, EX1080, ¶¶16-20. PO's argument that "masking" could cause a lower observed KIE than the 12-16-times slowing indicated by Roth, Itou, and Doering does not undermine REOS (EX1080, ¶¶52-54). No REOS is required for the natural result of this otherwise obvious prior-art combination. *Hospira*, 946 F.3d at 1332. Because substituting C₂₀-deuterated vitamin A equivalents into existing MD-treatment regimens was obvious, PO's argument that no REOS existed for the specific *degree* of slowing observed should be rejected.

E. PO's Secondary Considerations Are Not Probative

Secondary considerations lack probity for non-obviousness when created by a prior-art feature. *Yita LLC v. MacNeil IP LLC*, 69 F.4th 1356, 1364 (Fed. Cir. 2023); *Asyst Techs., Inc. v. Emtrak, Inc.*, 544 F.3d 1310, 1316 (Fed. Cir. 2008). Here, all PO's secondary considerations related to prior-art gildeuretinol/ALK-001. EX1069, 282:22-287:22; EX1006. The patent admits ALK-001 stability against the 1,5-shift naturally results from C₂₀-deuteration (Pet. 35-36), a prior-art feature. Orally administering daily vitamin A (including pro-vitamin A carotenoids) to MD patients also was in the prior art. *See* Section II.A above. Accordingly, PO finds no support for its non-obviousness arguments through secondary considerations.

Moreover, PO's secondary considerations are not commensurate in scope with its claims. None of its claims is directed to the protocol employed in all relied-upon clinical studies. EX1001, claims; EX1079, 135:9-139:11 (always at least 14 mg/day orally, 24 months); EX1069, 268:15-271:25 (always C₂₀-trideuterated retinyl acetate capsule). Most claims are not directed to Stargardt or ABCR-linked disease. EX1001, claims; EX1079, 131:13-25 (TEASE inclusion criteria require Stargardt 1 diagnosis).

The patent also lacks any claim reciting the specific and undisclosed formulation used in all PO's clinical trials. EX1001, claims; EX1069, 271:6-273:24 ("The excipients can be very important...so they can certainly have an

effect” but the patent is very open-ended on what formulations to use). PO maintains its trial details (including formulation) as trade secrets, and therefore forbade its witnesses from disclosing them (despite designating the confidential transcript Outside-Counsel-Eyes-Only). EX1079, 66:9-71:22. Of course, any treatment details too secret to share with the PTAB are not recited in the challenged claims, and therefore preclude nexus. Because PO withheld this evidence through its improper instructions, the Board should infer the evidence undermines PO’s assertions. *Gumbs v. Int’l Harvester, Inc.*, 718 F.2d 88, 96 (3d Cir. 1983); *see also* 37 C.F.R. §42.65 (no weight to studies when underlying data was not provided).

i. No Long-Felt, Unmet Need or Failure of Others

PO argues a long-felt need to develop human MD treatments, and failure of others to do so until ALK-001 filled the need, undermines REOS. POR 47-52. Curiously, PO labels the FDA-approved Geographic Atrophy (GA) AMD treatments as “failures,” while its own clinician trumpeted them as an earlier “success” that generated “much excitement” and “exuberance” and a “staggering” billion-dollar acquisition. EX1069, 248:8-253:22 (“Finally, we have a drug to treat [dry AMD]”); EX2171; *see also* EX1069, 230:20-233:17 (first FDA-approved treatments for GA (dry AMD)), 236:24-237:18 (statistically significant 27.4% reduction in growth rate), 240:6-242:20 (clinically meaningful); EX1066; EX1069,

247:22-248:2 (the “much needed therapeutic option” that became available to patients).

Even more curiously, PO trumpets ALK-001 as successfully treating GA while its own clinician admits the clinical trial failed. EX1069, 267:1-268:7 (“the SAGA trial was unable to report they met the prespecified primary endpoint”), 237:7-239:5 (clinical trial failing to satisfy primary endpoint with $p \leq 0.05$ is generally “regarded as a failure” and calling it a success “would be problematic”). With these admissions, PO’s argument cannot succeed.

PO’s preliminary Stargardt studies fare no better. PO’s clinician testified clinical trials should be conducted using qualified readers at independent reading centers, reading fully-masked images to prevent bias. EX1069, 224:7-225:20 (“It prevents somebody from saying oh, yeah, this drug appears to be working because they know that picture A actually came two years before picture B.”). Image scoring should be adjudicated independently before results are known or reported, and a sponsoring-company executive should never be adjudicating the images. EX1069, 225:21-227:18 (“In my opinion, that would not have been appropriate.”). But public documents indicate PO instead conducted “most of its actual science...in-house” and used inexperienced personnel (including undergraduate students). EX2179, 3; EX1074-EX1078 (unqualified interns); EX1079, 151:4-13, 181:7- 204:2 (same); [REDACTED]

[REDACTED]

[REDACTED]

[REDACTED] Though PO presented brief interim-result abstracts, a full, peer-reviewed publication of the study never followed. EX2086 (2016 abstract: “enrollment is ongoing”); EX2087 (2019 abstract: “interim” data; an “expanded study...is currently enrolling”); 228:20-230:2 (no evidence of peer-review submitted). PO never asserted a Phase 3 Stargardt study exists, much less has been completed successfully.

Neither PO’s interim-result reporting of three patients’ anecdotal experiences in an open-label, non-randomized study (TEASE 3, EX1079, 77:18-20, 117:20-23), nor any *post-hoc* arguments about its small Phase 2 study, can conjure a peer-reviewed publication of a successful Phase 3 study. PO’s interim TEASE 3 results rely on a misleading, apple-to-oranges comparison, and inherently-variable measures unacceptable for FDA approval. EX1087, 19 (study participants measured using standardized ETDRS BCVA were compared to older siblings’ Snellen acuity measurements; study participants *at study initiation* had better measurements than older sibling at the same age); EX1079, 81:4-84:25 (visual acuity is “inherently variable”); EX1069, 239:12-240:5 (BCVA not acceptable to FDA as primary endpoint); 258:21-260:5 (not reliable); EX1066, 583; EX1068, 1294; EX1082, 2 (“earlier you have symptoms, the faster you have

progression”). Because PO never obtained successful results, PO’s expert testified the need in Stargardt remains unfilled today. EX2192, ¶¶282 (“still none are available today”), 286 (same). PO’s Stargardt arguments thus fail.

For slowing lipofuscin formation, PO’s evidence never demonstrates failure of others; visual-cycle inhibition successfully reduced lipofuscin formation, but with unnecessary side-effects. *See* Section II.A above; EX1080, ¶¶33-34. This is why the prior art suggested specifically inhibiting the byproduct pathway. The literature also reflected optimism about slowing MD progression. EX1080, ¶¶72-73; EX2074, 11 (MDs are “disorders of homeostasis,” so there were “good reasons to be optimistic” that small reductions would delay vision loss by years), 5-6 (body was able to clear lipofuscin deposits); EX1069, 193:7-197:4 (lipofuscin deposits “really do come and go”). PO identifies no technical obstacle to using deuterated-vitamin A to retard lipofuscin formulation. Mechanistic studies leading to the critical date validated this ability to retard lipofuscin formation (EX1080, ¶30), so the literature declared in 2007 that the time had come specifically to retard the A2E-byproduct pathway (EX1080, ¶¶31-32) rather than induce blindness and serious side effects (EX1080, ¶¶33-36). Together with surging interest in deuterating known compounds in 2005-2007 (EX1080, ¶13), the evidence identifies a straightforward application of prior-art knowledge to a question that only recently came to the forefront.

PO argues unmet need for an *oral* AMD treatment, but this argument is not commensurate with the challenged claims, which are not limited to an oral AMD treatment. EX1001, claims. Indeed, the claims expressly cover intravitreal injection. EX1070, 72:1-74:17. Moreover no technical difficulty prevented developing oral medication. MD patients already took vitamin A orally. *See* Section II.A above; EX1022, Abstract (AMD); EX1069, 129:12-132:6 (Sorsby’s fundus and retinitis pigmentosa). Other oral medications were in development. EX2101, 4 (remofuscin reduced lipofuscin after “oral administration.”), 6 (remofuscin “stimulated the exocytosis of lipofuscin from the RPE...with no adverse effects”). PO identifies no technical barrier to oral MD therapies or any missing technical solution it provided. Nor could it, because ALK-001 existed long before the critical date. EX1006.

ii. PO’s Skepticism and Praise Arguments Fail

PO argues initial skepticism existed about treating MD with ALK-001. POR 53 (citing EX2180, 14; EX2179, 3; EX2161, 9). But PO’s asserted skepticism related to *humans* maintaining the “tight dietary control [that was] required to achieve these results in mice.” *E.g.*, EX2180, 14; EX2161, 7 (similar). The patent lacks any claim regarding dietary control or humans. EX1001, claims. In contrast, all TEASE studies excluded patients taking vitamin A or beta-carotene. EX1079, 133:16-135:7; EX2098; EX2099. PO’s exhibits thus express no skepticism

regarding any claim limitation. EX1070, 59:22-66:6 (claims treatment of rodents). Nor are they skeptical about the natural results of C₂₀-deuteration. They are irrelevant to obviousness.

PO's argument (POR 53) that venture capital firms asked for "human data" before investing (EX2179, 3) similarly address unclaimed features. PO's VC-funding-argument also is undermined by numerous public statements (e.g., Leonide Saad "was reluctant to relinquish control, so he largely stayed away from venture funding"). EX1081, 3; EX1084, 2-3 (Saad declared: "No, I want to do it myself."); EX1079, 208:4-209:9 (Saad simply forgot about these interviews).

PO asserts industry recognition via breakthrough and orphan designation and hopeful patient anecdotes. POR 53-54 (citing EX2107; EX2092; EX2182). By their own terms, breakthrough and orphan designations reflect *a desire* for successful results rather than a conclusion they were already obtained. EX2107, 2 ("primary intent" to "develop evidence needed to support approval"). As discussed above (Section II.E.i), PO's results remain preliminary, full results still lack peer-reviewed publication, and PO's expert confirmed the Stargardt treatment need remains unmet. *See also* EX1079, 230:3-231:9 (June 2023: data still not published in a peer-reviewed medical journal); EX1086, 2. Moreover, statements in a PO press release (EX2092) from a PO-commissioned author of a PO-commissioned

study (EX2091) cannot constitute industry praise. *In re Cree, Inc.*, 818 F.3d 694, 702 (Fed. Cir. 2016).

Finally, PO argues incongruously that the skepticism it allegedly faced was pre-dated by “praise” from Dr. Guengerich for PO’s “pre-clinical results.” POR, 54-55. Anyways, Dr. Guengerich explains the reviewer comments only reflect that the reviewers never performed a patentability analysis. EX1080, ¶78.

iii. PO’s Unexpected Results Argument Fails

PO argues C₂₀-deuterated vitamin A “has the surprising ability to reduce lipofuscin accumulation...without inducing night blindness or impaired dark adaptation.” POR 55-57. But inhibiting the A2E-byproduct pathway downstream of the visual cycle was expected to reduce A2E/lipofuscin accumulation without inducing night blindness or impaired dark adaptation. EX1004, ¶¶76-79, 243. That is precisely why the prior art suggested it. EX1080, ¶¶28-36. This property of the prior-art compound cannot be an unexpected result. EX1080, ¶35.

PO argues ALK-001 unexpectedly replaces normal vitamin A in the blood quickly. POR 56-57 (~90% of plasma concentration in 8 weeks). But the prior art disclosed administering comparably large vitamin A doses (e.g., 14 mg). *See* Section II.A above. PO never demonstrates supplemented vitamin A entering circulation this way was unexpected.

F. PO's Additional Arguments Fail

PO repeats its arguments against certain grounds and certain claims (POR 57-63), and these arguments fail as addressed above.

PO additionally argues against administering with phosphatidylglycerol and directly to the eye. POR 62-63. But the petition explains how Widder teaches phosphatidylglycerol benefits MD patients, citing prior-art teachings showing it protects RPE cells from A2E-induced apoptosis (ameliorating existing lipofuscin). Pet. 60-61; EX1002, ¶¶162-163, 313, 326-333; EX1004, ¶¶69-72, 121-122, 231-233; EX1009, 33:1-7; EX1020, Abstract, 537, 541-542; EX1021, Abstract. PO's attacks are groundless.

PO never contests that Widder discloses administration directly to the eye, but argues (POR 63) Wolf teaches night blindness "would not yield to topical treatment." Wolf also teaches that topically administering vitamin A supports cornea health, and that vitamin A diffuses through eye tissue. EX1028, 1.

Accordingly, local ocular delivery was useful to reduce lipofuscin formation without depriving ocular tissue of essential vitamin A. Pet. 64; EX1004, ¶¶57-59, 235-241. PO's argument should be rejected.

III. PO'S QUALIFICATION ATTACKS ARE MERITLESS

PO baselessly attacks Dr. Calman's qualifications because he refers Stargardt patients to a colleague for care. POR 10-11. PO's own clinician behaves

similarly. EX1069, 266:3-10. Dr. Calman's decades of relevant experience render him more than qualified. EX1004, ¶¶5-10 ("half of my patients have retinal or macular disease."); EX1005; EX2104, 10:21-12:11 (diagnoses and treats patients with retinal and macular disease and diagnoses Stargardt patients). PO's definition is so narrow that it excludes its sole inventor. EX1083 (PubMed lists no pre-critical date lipofuscin-biosynthesis publications for Dr. Washington); EX1079, 204:4-207:13 (Alkeus CSO refusing to answer questions about Dr. Washington's qualifications). It should be rejected. *Orthopediatrics Corp. v. Wishbone Med., Inc.*, 2022 U.S. Dist. LEXIS 181411, at *14-15 (N.D. Ind. Oct. 4, 2022) (hereinafter "*Orthopediatrics*").

PO also baselessly attacks Dr. Guengerich's qualifications. POR 12. But PO ignores that Dr. Guengerich's expertise (e.g., Ph.D. in Biochemistry, publications in retinoid and steroid biochemistry and deuteration) satisfies both parties' definitions. EX1002, ¶¶3, 5-6, 11-12; EX1003; EX1080, ¶¶14-15; EX1070, 28:11-12 (retinoids and steroids are terpenes), 42:15-43:7, 44:11-47:11, 49:20-51:11, 53:18-55:2 (published on steroids and retinoids and no dispute satisfies both definitions). PO's meritless qualification attacks should be rejected.

PO next argues it is improper to have both experts testify in a case about chemistry and ophthalmology. POR 9. But PO likewise defines the POSA to include multiple disciplines (medicine and/or chemistry) and offers testimony from

its own chemist and ophthalmologist. POR-7-8. Courts have routinely approved POSA definitions encompassing a multi-disciplinary team of experts.

Orthopediatrics at *14; *Pfizer, Inc. v. Teva Pharms. USA, Inc.*, 803 F. Supp. 2d 409, 442 (E.D. Va. 2011). PO's contrary arguments should be rejected.

IV. PO'S RPI ARGUMENT IS MERITLESS

PO alleges companies should be named as RPIs based on alleged "overlapping" personnel or investors. POR 63-64. But PO's executive signed his declaration identifying PO's RPIs while already aware of overlap between **PO's** management and board by its controlling investor, Bain Capital. EX1079, 158:3-174:6; EX1071-EX1073. PO failed to mention Bain's vested interest in its RPI disclosures, confirming such RPI arguments are baseless. They should be rejected.

V. CONCLUSION

The challenged claims should be cancelled.

Respectfully submitted,

Dated: December 23, 2024

/ Jad A. Mills /
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VI. CERTIFICATE OF COMPLIANCE

Pursuant to 37 C.F.R. §42.24(d), the undersigned certifies that this Reply complies with the type-volume limitation of 37 C.F.R. §42.24(c). The word count application of the word processing program used to prepare this Reply indicates that the Reply contains 5,575 words, excluding the parts of the brief exempted by 37 C.F.R. §42.24(c).

Respectfully submitted,

Dated: December 23, 2024

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VII. APPENDIX – PETITIONER’S UPDATED EXHIBIT LIST

Exhibit No.	Description
1001	U.S. Patent No. RE47,045 to Washington et al.
1002	Declaration of Dr. F. Peter Guengerich.
1003	<i>Curriculum Vitae</i> of Dr. F. Peter Guengerich.
1006	Robert Bergen, H., Furr, H. C., & Olson, J. A., Synthesis of Tri-, Tetra-, and Penta-deuterated Forms of Vitamin A, <i>Journal of Labelled Compounds and Radiopharmaceuticals</i> , 25(1), 11-21 (1988) (“Olsen 1988”).
1007	Furr, H. C., Amedee-Manesme, O., Clifford, A. J., Bergen 3rd, H. R., Jones, A. D., Anderson, D. P., & Olson, J. A., Vitamin A concentrations in liver determined by isotope dilution assay with tetradeuterated vitamin A and by biopsy in generally healthy adult humans, <i>The American Journal of Clinical Nutrition</i> , 49(4), 713-716 (1989) (“Olson 1989”)
1008	DE202006014588U1 (English Translation) (“Ortho Pharma”)
1009	WO 2006/007314 to Widder et al. (“Widder”)
1010	Mata, N. L. et al., Biosynthesis of a major lipofuscin fluorophore in mice and humans with ABCR-mediated retinal and macular degeneration, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 97(13), 7154-7159 (2000) (“Mata”)
1011	Fishkin et al., Isolation and Characterization of a Retinal Pigment Epithelial Cell Fluorophore: An All-trans-retinal Dimer Conjugate, <i>Proceedings of the National Academy of Sciences of the United States of America</i> , 102(20), 7091-7096 (2005) (“Fishkin”)
1012	Haskins, N. J., The Application of Stable Isotopes in Biomedical Research, <i>Biomedical Mass Spectrometry</i> , 9(7), 269-277 (1982) (“Haskins”)

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1013	Baillie, T. A., The Use of Stable Isotopes in Pharmacological Research, <i>Pharmacological Reviews</i> , 33(2), 81-132 (1981) (“Baillie”)
1014	Van Langenhove, A., Isotope Effects: Definitions and Consequences for Pharmacologic Studies, <i>The Journal of Clinical Pharmacology</i> , 26(6), 383-389 (1986) (“Langenhove”)
1015	Roth and König, Kinetic Isotope Effect of the 1.5-Hydrogen Displacement in <i>cis</i> -Pentadiene-(1.3), <i>Justus Liebigs Annalen Der Chemie</i> (1966) (“Roth”).
1016	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. <i>The Journal of Physical Chemistry A</i> , 111(2), 261-267 (2007) (“Itou”)
1017	Remington: The Science and Practice of Pharmacy, 19th ed. (1995) (chs. 80 & 89) (“Remington”)
1018	Parish et al., Isolation and One-step Preparation of A2E and Iso-A2E, Gluorophores from Human Retinal Pigment Epithelium, <i>Proceedings of the National Academy of Sciences</i> , 95(25), 14609-14613 (1998) (“Parish”)
1019	Furr et al. Stable Isotope Dilution Techniques for Assessing Vitamin A Status and Bioefficacy of Provitamin A Carotenoids in Humans, <i>Public Health Nutrition</i> , 8(6), 596-607 (2005) (“Furr”)
1020	Shaban & Richter, A2E and Blue Light in the Retina: The Paradigm of Age-related Macular Degeneration, <i>Biol. Chem.</i> , 383(3-4), 537-45 (2002) (“Shaban & Richter”)
1021	Shaban et al., Phosphatidylglycerol Potently Protects Human Retinal Pigment Epithelial Cells Against Apoptosis Induced by A2E, a Compound Suspected to Cause Age-related Macula Degeneration, <i>Experimental eye research</i> , 75(1), 99-108 (2002) (“Shaban”)
1022	Age-Related Eye Disease Study Research Group, A Randomized, Placebo-controlled, Clinical Trial of High-dose Supplementation with Vitamins C and E, Beta Carotene, and

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	Zinc for Age-related Macular Degeneration and Vision Loss: AREDS report no. 8. <i>Archives of Ophthalmology</i> , 119(10), 1417-1436 (2001) (“AREDS”)
1031	File History of U.S. Patent Application No. 12/733,631
1032	File History of U.S. Patent Application No. 14/510,975
1035	Radu, Roxana A. et al. “Treatment with Isotretinoin Inhibits Lipofuscin Accumulation in a Mouse Model of Recessive Stargardt’s Macular Degeneration.” <i>Proceedings of the National Academy of Sciences of the United States of America</i> 100:4742-4747 (2003) (“Radu”)
1050	Kuksa V, Imanishi Y, Batten M, Palczewski K, Moise AR. Retinoid Cycle in the Vertebrate Retina: Experimental Approaches and Mechanisms of Isomerization, <i>Vision Res.</i> 43(28):2959-81 (2003) (“Kuksa”)
1051	Miwa, GT & Lu, AY, Kinetic Isotope Effects and ‘Metabolic Switching’ in Cytochrome P450-catalyzed Reactions, <i>BioEssays</i> , 7(5), 215-219 (1987) (“Miwa”)
1052	WO 95/04018 to Marcus F. Boehm (“Boehm”)
1057	File History resulting in U.S. Reissue Patent No. RE47,045
1058	Duszka, et al., Rat Intestinal β -Carotene Dioxygenase Activity Is Located Primarily in the Cytosol of Mature Jejunal Enterocytes. <i>Nutrient Metabolism</i> 2550-2556 (1996).
1059	American Optometric Association, “Care of the Patient with Age-Related Macular Degeneration,” Optometric Clinical Practice Guideline (2004).
1060	First Supplemental Declaration of Irina Hinrichs (supplemental evidence for EX1023) (SERVED NOT FILED)
1061	Second Supplemental Declaration of Irina Hinrichs (supplemental evidence for EX1024) (SERVED NOT FILED)
1062	Age-Related Eye Disease Study Research Group, A Randomized, Placebo-controlled, Clinical Trial of High-dose Supplementation with Vitamins C and E, Beta Carotene, and Zinc for Age-related Macular Degeneration and Vision Loss: AREDS report no. 8. <i>Archives of Ophthalmology</i> , 119(10),

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	1417-1436 (2001) (supplemental evidence for EX1022) (SERVED NOT FILED)
1063	Wolf, G., A History of Vitamin A and Retinoids. The FASEB Journal, 10: 1102-1107 (1996) (supplemental evidence for EX1028) (SERVED NOT FILED)
1064	Bull E., What is a Nutraceutical? Pharm J. 265:57-58 (2000) (supplemental evidence for EX1049) (SERVED NOT FILED)
1065	Centrum Silver Adults Label (200 Tablets) Multivitamin
1066	Glenn J. Jaffee, et al., “ <i>C5 Inhibitor Avacincaptad Pegol for Geographic Atrophy Due to Age-Related Macular Degeneration, Ophthalmology</i> ”, Volume 128, Issue 4, 576 - 586
1067	Jeffrey S. Heier, et al., “ <i>Pegcetacoplan for the treatment of geographic atrophy secondary to age-related macular degeneration (OAKS and DERBY): two multicentre, randomised, double-masked, sham-controlled, phase 3 trials</i> ”, Lancet 2023; 402: 1434–48
1068	Liangbo L. Shen et al., “ <i>Natural History of Autosomal Recessive Stargardt Disease in Untreated Eyes</i> ”, Ophthalmology, Volume 126, Issue 9, 1288 - 1296
1069	Deposition Transcript of Lucian Del Priore (November 13, 2024)
1070	Deposition Transcript of Glenn D. Prestwich, Ph.D. (November 15, 2024)
1071	Alkeus Pharmaceuticals Inc - Transformation in Sight, https://alkeuspharma.com (last visited Oct. 25, 2024)
1072	Bain Capital - Current and former portfolio companies, available from https://www.baincapitalprivateequity.com/portfolio/current-and-former-portfolio-companies (last visited Nov. 21, 2024)
1073	Alkeus Pharmaceuticals Inc - Transformation in Sight, https://alkeuspharma.com (last visited Nov. 21, 2024)
1074	LinkedIn Profile for Michael Song (last visited Nov. 21, 2024)
1075	LinkedIn Profile for Monica Hennessey (last visited Nov. 20, 2024)

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1076	LinkedIn Profile for Christine Xu (last visited Nov. 21, 2024)
1077	LinkedIn Profile for Cyriac Joyce (last visited Nov. 21, 2024)
1078	LinkedIn Profile for Runyao Tung (last visited Nov. 21, 2024)
1079	CONFIDENTIAL and PUBLIC REDACTED VERSIONS– Deposition Transcript of Leonide Saad Ph.D. (November 26, 2024)
1080	Rebuttal Declaration of Dr. F. Peter Guengerich
1081	Ben Fidler, “ <i>An unconventional drug startup lures Vertex founder Josh Boger back to biotech,</i> ” BioPharmaDive (Jun. 5, 2023), available from https://www.biopharmadive.com/news/alkeus-biotech-startup-josh-boger-stargardt/651949/ (last visited Dec. 20, 2024)
1082	Jonathan Saltzman, “ <i>Cambridge biotech raises \$150 million and rehires founder of Vertex,</i> ” Boston Globe (Jun. 5, 2023) available from https://www.bostonglobe.com/2023/06/05/business/alkeus-pharmaceuticals-raises-150-million/ (last visited Dec. 19, 2024)
1083	Ilyas Washington, PubMed Publication Entries, 2001-2007, available from https://pubmed.ncbi.nlm.nih.gov/?term=Ilyas+Washington&filter=years.2001-2004&sort=pubdate (last visited Dec. 19, 2024)
1084	Rowan Walrath, “ <i>Vertex founder Josh Boger is back in biotech. Here’s why he ‘unretired.’</i> ” Boston Business Journal (Jun. 11, 2023), available from https://www.bizjournals.com/boston/news/2023/06/12/alkeus-vertex-josh-boger-un-retirement.html (last visited Dec. 19, 2024)
1085	Screenshot of https://timmermanreport.com/2023/06/alkeus-a-bootstrap-success-story-graduates-with-150m-series-b/ - Luke Timmerman, “ <i>Alkeus, A Bootstrap Success Story, Grows Up With \$150M Series B</i> ”, Timmerman Report (Jun. 2023), available from Timmerman Report.com (last visited Dec. 19, 2024)
1086	Luke Timmerman, “ <i>Alkeus, A Bootstrap Success Story, Grows Up With \$150M Series B</i> ”, Timmerman Report (Jun. 2023), available from Timmerman Report.com

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1087	Christine N. Kay, MD; Leonide Saad; Gabrielle DeBartolomeo; Ilyas Washington; Philip J. Ferrone; Hendrik P. Scholl; Marc T. Mathias; “Gildeuretinol Slows Progression of Stargardt Disease The TEASE Program, Presented at the Annual Meeting of the American Academy of Ophthalmology (AAO), Chicago, IL (Oct. 20, 2024).
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CERTIFICATE OF SERVICE

The undersigned certifies that the foregoing Petitioner's Reply to Patent Owner's Response and Exhibits 1065-1087 were served on December 23, 2024, at the following electronic service addresses:

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