

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. IPR2024-00312
Patent No. 9,486,432

DECLARATION OF DR. ANDREW CALMAN, M.D., PH.D.

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I, Dr. Andrew Calman, M.D., PhD. declare as follows:

I. QUALIFICATIONS

1. I have been retained by Counsel on behalf of Gene Company Pty Ltd (Gene Company) to provide opinions in this matter related to my experience and expertise. My opinions are based on my skills, knowledge, training, education, and experience in matters of this nature, and my examination of the materials utilized in preparing this report.

2. I am a board-certified ophthalmologist serving at Premier Eyecare of San Francisco, an ophthalmology practice in San Francisco. I am also an Associate Clinical Professor of Ophthalmology at University of California, San Francisco, and a Clinical Faculty Member in Ophthalmology at California Pacific Medical Center.

3. I received my Bachelor of Science in Molecular Biophysics and Biochemistry, *summa cum laude*, from Yale University in 1982, with Distinction in the Major. I also received my Master of Science in Molecular Biophysics and Biochemistry from Yale University in 1982. I then attended medical school and graduate school at the University of California, San Francisco (UCSF) with a full scholarship from the Medical Scientist Training Program of the National Institutes of Health from 1982 to 1989. In 1989, I received my Doctor of Medicine (M.D.) and Doctor of Philosophy (Ph.D.) in Microbiology and Immunology from UCSF,

earning the Dean's Prize for Student Research, a Chancellor's Fellowship, membership in Alpha Omega Alpha, and the E. E. Osgood Award for best student biomedical research in the Western United States.

4. From 1989-1990, I completed a one-year internship in Internal Medicine at Kaiser Foundation Hospital in San Francisco, followed by a three-year residency in Ophthalmology at UCSF. During this time, I set up a molecular biology laboratory in the Department of Ophthalmology at UCSF, resulting in the cloning of a human cataract gene by genetic complementation of galactokinase-deficient yeast cells.

5. I have been on the clinical faculty of UCSF since 1993, with a current appointment as Associate Clinical Professor of Ophthalmology. For many years I also held a joint appointment in the Department of Family and Community Medicine at UCSF. I also hold a faculty appointment at California Pacific Medical Center (CPMC). My teaching activities at these academic institutions include training residents and medical students in diagnosis and treatment of eye disease, such as macular degeneration, coordinating the resident Journal Club at CPMC, and teaching ophthalmic surgery. In addition, international medical students from the Netherlands, Thailand, the Philippines, Mexico, and Colombia have trained in my office, in preparation for residency training in ophthalmology.

6. I was board certified in ophthalmology in 1994 and recertified in 2004 and 2014. Since 1997, I have served as an Associate Examiner for the American Board of Ophthalmology (ABO), administering the Oral Board Examination for candidates for board certification. In this capacity I have examined candidates in multiple subspecialty areas within ophthalmology, most recently in Retinal Disease and Neuro-Ophthalmology in 2021. I also serve on the question-writing panel for the ABO.

7. From 1996 to 2004, I served on the Medicare Carrier Advisory Committee for California and several other states, helping to formulate and review Medicare policies on various ophthalmic conditions and procedures, including those involving macular degeneration. I held a similar position at the national level from 2004 to 2008, serving on the Health Policy Committee of the American Academy of Ophthalmology. In 2010, I served as President of the California Academy of Eye Physicians and Surgeons (known at that time as the California Academy of Ophthalmology), which is the state professional society for California ophthalmologists. In addition to these and other leadership positions in professional societies at the local, state and national level, I am Past Chairperson of Prevent Blindness California, a non-profit dedicated to finding and treating cases of preventable vision loss in children and adults.

8. Since 1993, I have had a busy comprehensive ophthalmology practice in the Mission District of San Francisco, diagnosing and treating a diverse, high-pathology population for a variety of ophthalmic conditions, including macular degeneration. Approximately half of my patients have retinal or macular disease.

9. I have published more than 20 original scientific articles in periodicals, such as *Nature*, *Proceedings of the National Academy of Sciences*, *Ophthalmology Retina*, *Journal of Experimental Medicine*, *Journal of Immunology*, and *San Francisco Medicine*. I have participated in clinical research in the diagnosis and treatment of retinal disease. Furthermore, I am the recipient of the American Academy of Ophthalmology Achievement Award (2009) and the American Academy of Ophthalmology Special Recognition Award (2013).

10. I have attached as EX1005 a copy of my *Curriculum Vitae*, which provides additional details about my education, experience, publications, and other qualifications to render an expert opinion in this matter.

II. SCOPE OF WORK

11. I understand that a petition is being filed with the United States Patent and Trademark Office for Inter Partes Review of U.S. Patent No. 9,486,432 to Ilyas Washington (“the ’432 patent,” attached as EX1001), entitled “Compositions and Methods for Treating Macular Degeneration.” I understand that the ’432 patent is assigned to The Trustees of Columbia University in the City of New York.

12. I have been retained by Gene Company Pty Ltd (“Gene Company”) to offer an expert opinion on the validity of claims 1-28 of the ’432 patent. I receive \$750 per hour for my services preparing this declaration. No part of my compensation is dependent on my opinions or on the outcome of this proceeding.

13. I have been specifically asked to provide my opinion evaluating the patentability of claims 1-28 of the ’432 patent as of September 12, 2007 (the earliest claimed priority date, sometimes called the critical date). In connection with this analysis, I have reviewed the ’432 patent. I have also reviewed and considered various other documents in arriving at my opinions and cite them in this declaration.

III. LEGAL STANDARDS

14. I understand from Counsel that the United States Patent Office may cancel issued claims of the ’432 patent if the Petitioner (here, Gene Company) demonstrates that the claims fail to satisfy the requirements of patentability that the claims must be novel and non-obvious. I understand from Counsel that the claims should be understood according to their ordinary and customary meaning as understood by a person of ordinary skill in the art (“POSA”) at the time of the invention in light of the language of the claims, the specification, and the prosecution history of record. I have been provided a copy of the prosecution

history of the '432 patent and its parents application, which are identified as EX1031-EX1032.

A. Anticipation

15. I understand from Counsel that anticipation requires disclosure in a single reference of every element of a claim, I understand from Counsel that prior art disclosure of a species anticipates a genus that encompasses the species, that prior art disclosure of a point in a claimed range anticipates the claimed range, and that prior art disclosure of a range overlapping with a claimed range anticipates the claimed range where no criticality has been demonstrated for the claimed range.

B. Obviousness

16. I understand from Counsel that a claimed invention is unpatentable for obviousness if the differences between the invention and the prior art are such that the subject matter as a whole would have been obvious to a person of ordinary skill in the art at the time the invention was made (i.e., at the critical date).

17. It is further my understanding from Counsel that a determination of obviousness requires inquiries into: (1) the scope and contents of the prior art when the invention was made; (2) the differences between the prior art and the claims at issue; (3) the level of ordinary skill in the pertinent art when the invention was made; and, to the extent they exist, (4) secondary indicia of obviousness.

18. I understand from Counsel that a claim is obvious if all of the claimed elements were known in the prior art and one skilled in the art would have had a motivation to combine the elements as claimed with a reasonable expectation of success. I understand from Counsel that obviousness may also be shown by demonstrating that it would have been obvious to modify what is taught in a single piece of prior art to create the patented invention or by combining teachings of two or more references. I understand from Counsel that in order for a claimed invention to be considered obvious based on a combination of prior art references, there must be some rational underpinning for the proposed combination. I understand from Counsel that improper hindsight must not be used when determining whether a person of ordinary skill in the art would make the proposed combination; thus, a conclusion of obviousness must be firmly based on knowledge and skill of a person of ordinary skill in the art at the time the invention was made without the improper use of post-filing knowledge.

19. In determining whether a particular combination of prior art teachings would have been obvious, I understand from Counsel that the following are examples of approaches and rationales that may be considered:

- (a) Combining prior art elements according to known methods to yield predictable results;

- (b) Simple substitution of one known element for another to obtain predictable results;
- (c) Use of a known technique to improve similar devices (methods, or products) in the same way;
- (d) Applying a known technique to a known device (method, or product) ready for improvement to yield predictable results;
- (e) Applying a technique or approach that would have been “obvious to try” (choosing from a finite number of identified, predictable solutions, with a reasonable expectation of success);
- (f) Known work in one field of endeavor may prompt variations of it for use in either the same field or a different one based on design incentives or other market forces if the variations would have been predictable to one of ordinary skill in the art; or
- (g) Some teaching, suggestion, or motivation in the prior art that would have led one of ordinary skill to modify the prior art reference or to combine prior art reference teachings to arrive at the claimed invention.

20. I understand from Counsel that obviousness may be established by showing that all of the claimed elements were known in the prior art and that a person skilled in the art would have combined the elements as claimed by known methods with no change in their respective functions, and the combination would

have yielded nothing more than predictable results to one of ordinary skill in the art.

IV. OVERVIEW OF THE '432 PATENT

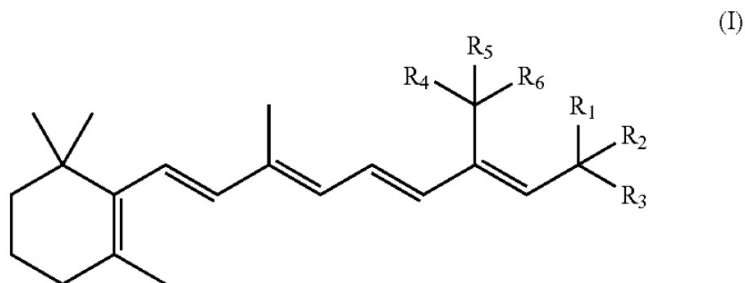
21. I have reviewed the '432 patent in its entirety including the specification, the figures, and the claims. The title of the '432 patent is “Compositions and Methods for Treating Macular Degeneration.” The Abstract of the '432 patent states:

Methods of retarding formation of a lipofuscin pigment in the retina and of treating or ameliorating the effects of a disease characterized by an accumulation of a lipofuscin pigment in a retina are provided. These methods include the step of administering to a patient in need thereof a substituted C₂₀-retinoid in an amount sufficient to reduce accumulation of a lipofuscin pigment in the retina. Further provided are methods of retarding formation of A2E and/or ATR-dimer by replacing an all-trans-retinal (ATR) substrate with a C₂₀-D₃-retinal substrate under conditions sufficient to impede the formation of A2E. Compositions for retarding formation of a lipofuscin pigment in the retina containing a substituted C₂₀-retinoid and a pharmaceutically acceptable carrier are also provided.

EX1001 (the '432 patent), Abstract. For this quote, and throughout my declaration, I have omitted internal citations unless otherwise stated.

22. Among other substituted C₂₀-retinoids, the '432 patent discusses substituting one, two, or three of the hydrogen atoms at C₂₀ with fluorine or deuterium. For example, the '432 patent discloses “a composition comprising a pharmaceutically acceptable carrier and a compound according to formula I.”

EX1001 (the '432 patent), 5:42-44. Formula I of the '432 patent is reproduced below.



wherein:

R_1 is oxo or H;

R_2 is H or nothing;

R_3 is hydroxy or oxo or CHR_7 where R_7 forms a carotenoid and

R_4 , R_5 , and R_6 are independently selected from the group consisting of ^1H , ^2H , ^3H , halogen, and C_{1-8} alkyl.

EX1001 (the '432 patent), 5:42-62.

23. The '432 patent does not disclose any experiments to demonstrate the safety of chronic administration of C_{20} -deuterated retinoids, but instead assumes that they are non-toxic based on the decades of use of deuterated vitamin A in humans. For example, the '432 patent states: "Deuterated vitamin A is widely used in humans and shows no toxicity. Thus, a treatment using a C_{20} - D_{1-3} -retinoid should be an effective and non-toxic therapy to treat or ameliorate macular degeneration without adverse visual effects." EX1001 (the '432 patent), 8:17-21.

24. The '432 patent does not assert that the ability to formulate C_{20} -deuterated retinoids is an inventive aspect of the patent, instead conceding that

formulation of the claimed compounds is a “conventional” task that “is within the skill of the art.” For example, the patent states:

Effective dosage forms, modes of administration, and dosage amounts, in addition to those disclosed above, *may be determined empirically*, and making such determinations is *within the skill of the art*.

EX1001 (the '432 patent), 14:31-34. In this quote and throughout my declaration, all bold and italic emphases are added unless stated otherwise.

25. Consistent with its statement that modes of administration will be determined empirically using conventional knowledge within the skill in the art, the '432 patent lists a variety of administration means, including orally by ingestion or by direct administration to the eyes.

A compound of the present invention *may be administered in any desired and effective manner*: as pharmaceutical compositions for oral ingestion, or as an ointment or drop for local administration to the eyes, or for parenteral or other administration in any appropriate manner such as intraperitoneal, subcutaneous, topical, intradermal, inhalation, intrapulmonary, rectal, vaginal, sublingual, intramuscular, intravenous, intraarterial, intrathecal, or intralymphatic. Further, a compound of the present invention may be administered in conjunction with other treatments. A compound or composition of the present invention maybe encapsulated or otherwise protected against gastric or other secretions, if desired.

EX1001 (the '432 patent), 14:49-56. The '432 provides no data or evaluation of the effects of any kind of local administration of the claimed composition.

26. The '432 patent, citing Remington (EX1017), further states that the compound may be formulated into pharmaceutically acceptable dosage forms by conventional methods that are known to persons skilled in the art.

Regardless of the route of administration selected, the compounds of the present invention are formulated into pharmaceutically-acceptable dosage forms by *conventional methods known to those of skill in the art*. See, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.).

EX1001 (the '432 patent), 15:3-8.

27. Again citing Remington, the '432 patent further states that pharmaceutically acceptable carriers are well known in the art, determined using ordinary skill, and include water, saline solution, and corn oil.

Pharmaceutically acceptable carriers are well known in the art (see, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, *water, aqueous solutions* (e.g., *saline*, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides [*sic*]), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, *oils* (e.g., *corn*, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate [*sic*], etc. Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not

injurious to the subject. Carriers suitable for a selected dosage form and intended route of administration are *well known in the art*, and acceptable carriers for a chosen dosage form and method of administration can be *determined using ordinary skill in the art*.

EX1001 (the '432 patent), 15:9-27.

28. The '432 patent further discloses additional ingredients and materials known in the art that are commonly used with the pharmaceutical compositions, vitamin supplements, or nutraceuticals claimed. For example, the '432 patent discloses:

The pharmaceutical compositions or vitamin supplements or nutraceuticals of the invention may, optionally, contain additional ingredients and/or materials commonly used in such pharmaceutical compositions or vitamin supplements or nutraceuticals. These ingredients and materials are well known in the art and include (1) fillers or extenders, such as starches, lactose, sucrose, glucose, mannitol, and silicic acid; (2) binders, such as carboxymethylcellulose, alginates, gelatin, polyvinyl pyrrolidone, hydroxypropylmethyl cellulose, sucrose and acacia; (3) humectants, such as glycerol; (4) disintegrating agents, such as agar-agar, calcium carbonate, potato or tapioca starch, alginic acid, certain silicates, sodium starch glycolate, cross-linked sodium carboxymethyl cellulose and sodium carbonate; (5) solution retarding agents, such as paraffin; (6) absorption accelerators, such as quaternary ammonium compounds; (7) wetting agents, such as cetyl alcohol and glycerol monostearate [*sic*]; (8) absorbents, such as kaolin and bentonite clay; (9) lubricants, such as talc, calcium stearate, magnesium stearate, solid polyethylene glycols, and sodium lauryl sulfate; (10) suspending agents, such as ethoxylated isostearyl alcohols, polyoxyethylene sorbitol and sorbitan esters, microcrystalline cellulose, aluminum metahydroxide, bentonite, agar-agar and tragacanth; (11) buffering agents; (12) excipients, such as lactose, milk sugars, polyethylene glycols, animal and vegetable fats, oils, waxes, paraffins, cocoa butter, starches, tragacanth, cellulose derivatives, polyethylene glycol, silicones, bentonites, silicic acid, talc, salicylate, zinc oxide,

aluminum hydroxide, calcium silicates, and polyamide powder; (13) inert diluents, such as water or other solvents; (14) preservatives; (15) surface-active agents; (16) dispersing agents; (17) control-release or absorption-delaying agents, such as hydroxypropylmethyl cellulose, other polymer matrices, biodegradable polymers, liposomes, microspheres, aluminum monostearate [*sic*], gelatin, and waxes; (18) opacifying agents; (19) adjuvants; (20) wetting agents; (21) emulsifying and suspending agents; (22), solubilizing agents and emulsifiers, such as ethyl alcohol, isopropyl alcohol, ethyl carbonate, ethyl acetate, benzyl alcohol, benzyl benzoate, propylene glycol, 1,3-butylene glycol, oils (in particular, cottonseed, groundnut, corn, germ, olive, castor and sesame oils), glycerol, tetrahydrofuryl alcohol, polyethylene glycols and fatty acid esters of sorbitan; (23) propellants, such as chlorofluorohydrocarbons and volatile unsubstituted hydrocarbons, such as butane and propane; (24) antioxidants; (25) agents which render the formulation isotonic with the blood of the intended recipient, such as sugars and sodium chloride; (26) thickening agents; (27) coating materials, such as lecithin; and (28) sweetening, flavoring, coloring, perfuming and preservative agents.

EX1001 (the '432 patent), 15:37-66 and 16:1-19.

29. The '432 patent claims are directed to a pharmaceutical composition comprising a C₂₀-deuterium substituted retinoid in any pharmaceutically acceptable carrier.

30. I have reproduced the language of claim 1 here:

1. A pharmaceutical composition comprising
a substituted C₂₀-D₁₋₃-retinoid and
a pharmaceutically acceptable carrier,
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 a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

31. Each of claims 2-28 depends directly or indirectly from claim 1. The text of each of claims 2-28 is provided in Sections XI.B-D, XII.B-L, and XIII.A-C. below. As indicated by dependent claim 27, the pharmaceutical composition may be satisfied by a nutraceutical composition (such as a dietary supplement).

V. PROSECUTION HISTORY OF THE '432 PATENT

32. I understand from the face of the '432 patent that it claims priority to U.S. Provisional Patent Application No. 60/993,379, filed on Sep. 12, 2007, through U.S. Application Nos. 14/510,975 (filed on October 9, 2014) and 12/733,631 (filed as PCT/US2008/010676 on September 12, 2008). For purposes of my opinions, I have assumed that the claims are entitled to a priority date of September 12, 2007.

33. During prosecution of the '432 patent claims, the Examiner did not assert any prior art-based rejections. EX1032, (file history of the '975 application), 40-41. During prosecution of its parent '631 application, the Examiner asserted Radu (EX1035) and Boehm (EX1052). EX1031 (file history of the '631 application), 240-242; *see also id.* (additionally citing two patent publications, WO2005/065669 to Lang et al. and US2007/0015827 to Widder et al., a different application than the Widder (EX1009) discussed herein). During prosecution, the patent applicant noted that the claims “specifically exclude isotretinoin, the

pharmacological active agent tested by Radu.” EX1031 (file history of the ’631 application), 167. The patent applicant further stated that:

Although Radu teaches that 13-*cis*-retinoic acid (also known as isotretinoin), a non-substituted retinoid, inhibits formation of A2E dimers and lipofuscin, isotretinoin however does so by a very different mechanism than retinoids deuterated at the C₂₀ position. Isotretinoin is a retinoid that inhibits lipofuscin accumulation by slowing the visual cycle, which is known to lead to side effects such as night blindness and slowed dark adaptation. Radu specifically writes that “isotretinoin (Accutane) has been shown to slow the synthesis of 11-*cis*-retinaldehyde and regeneration of rhodopsin by inhibiting 11-*cis*-retinol dehydrogenase in the visual cycle.”

EX1031 (file history of the ’631 application), 167.

34. The patent applicant further argued that:

Applicant discovered that instead of inhibiting the visual cycle, the described C₂₀-deuterated retinoids (excluding at least isotretinoin and retinylamine, which would inhibit the retinoid pathway), could replace vitamin A with a C₂₀-deuterated vitamin A, which in itself would dimerize in the eye more slowly than non-deuterated vitamin A, because deuterium atoms are lost more slowly from the C₂₀ position than protium during vitamin A dimerization.

EX1031 (file history of the ’631 application), 168.

35. Regarding Boehm, the Examiner stated that “Boehm discloses a substituted C₂₀ retinoid. Tritium labeled is taught in page 5, line 13-19, formula V, and deuterium labeled is taught on page 6, lines 15-37.” EX1031 (file history of the ’631 application), 240. The Examiner, referring to Boehm, further stated that:

It would have been obvious to a person skilled in the art to use the labeled retinoids instead of retinoid for the inhibition of lipofuscin and treat a disease, such as, stargardt’s characterized by lipofuscin

accumulation and to improve efficacy of treatment, motivated by Boehm, which teaches the advantage of radio labeled retinoid in binding to the retinoid receptors.

EX1031 (file history of the '631 application), 240-241.

36. The patent applicant responded by arguing that Boehm does not disclose a C₂₀ deuterated retinoid. For example, the patent applicant stated that “[w]hile it is true that Boehm discloses a labeled retinoid, the labeling is not at the C₂₀ position but at the C₁₁ position, and such labeled retinoids do not fall into the claimed genus, retinoid specifically substituted at the carbon C₂₀ position with deuterium.” EX1031 (file history of the ‘631 application), 168. The patent applicant further stated that:

In this application, the Applicant discloses retinoids selectively substituted at the retinoid’s carbon number 20, the C₂₀ position. In particular, the claims currently amended focus only on retinoids whereby the protium (¹H or H) at the carbon 20 position have been replaced with deuterium (²H or D).

EX1031 (file history of the '631 application), 156. Unlike Radu and Boehm, Olson 1988, which I discuss more fully below (see Section X.A.), discloses claimed C₂₀-deuterated vitamin A.

37. I also read in the prosecution history of the '631 application that the patent applicant argued that Boehm provided no reason to make the C₂₀ substitution. For example, the patent applicant stated that “tritium or deuterium in any position other than C₂₀ would not be expected to have any effect on A2E or

lipofuscin formation.” EX1031 (file history of the ’631 application), 169. The patent application further stated that:

Besides, Boehm provides no guidance with respect to how to modify the tritium or deuterium labeled retinoids disclosed therein to obtain a deuterium or tritium labeled retinoid that could slow A2E formation. In particular, Boehm provides no reason to think that substituting deuterium at position 20 would reduce lipofuscin accumulation or lead to any other desirable result. Thus, Boehm provides no motivation to modify Radu’s isotretinoin by substituting deuterium at position 20.

EX1031 (file history of the ’631 application), 169-170. Unlike Boehm, Mata, which I discuss in more fully below in Section X.E., expressly shows that lipofuscin is formed by removal of a hydrogen from the C₂₀ of vitamin A and expressly suggests pharmacologically inhibiting this synthesis pathway to provide an effective treatment for macular degeneration.

VI. LEVEL OF SKILL IN THE ART

38. I have been advised by Counsel that “a person of ordinary skill in the art” (POSA) is a hypothetical person to whom one could assign a routine task with reasonable confidence that the task would be successfully carried out. I have been advised by Counsel further that, in determining the level of ordinary skill in the art that someone would have had at the time the claimed invention was made, I should consider: (1) the levels of education and experience of persons working in the field; (2) the types of problems encountered in the field; and (3) the sophistication of the technology.

39. A passage in the '432 patent states that “the present invention relates, inter alia, to compounds, compositions, and methods to slow lipofuscin formation/accumulation in order to treat or ameliorate an ophthalmologic disorder, such as, e.g., macular degeneration, without, or with reduced, adverse visual effects.” EX1001, 1:18-22. The '432 patent also states that the compounds “may be used to treat or ameliorate an ophthalmologic disorder, such as e.g., macular degeneration, by slowing or limiting the accumulation of age pigments or lipofuscin in the retinal pigment epithelium (‘RPE’) cells of the retina.” EX1001, 1:24-28. As I explained above, the patent claims are directed to deuterated forms of Vitamin A (e.g., retinol, retinol esters, retinal, and pro-vitamin A carotenoids) in a pharmaceutically acceptable carrier.

40. Based on my specialized education, knowledge, training, and experience, I am familiar with the level of skill of a person of ordinary skill in the art of treating lipofuscin-associated diseases such as macular degeneration as of the critical date. It is my opinion that a person of ordinary skill in the art of the '432 patent in September 2007 would be part of an interdisciplinary team. Members of the team would have had 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. It is my opinion that this team would have included a practicing physician who diagnoses

and treats ophthalmologic disorders, such as macular degeneration, together with a biochemist or a chemist familiar with deuterated compounds, including those formulated for administration. My specialized education, knowledge, training, skills, and experience qualify me to opine on the knowledge and perspective of a person of ordinary skill in the art from the perspective of a clinician who diagnoses and treats ophthalmologic disorders.

VII. SUMMARY OF OPINIONS

41. As I will explain in detail below, and relying where appropriate on the opinions of Dr. Guengerich: 1) The teachings of Olson 1988 and Olson 1989 render obvious each of claims 1-6 and 28 of the '432 patent; 2) The teachings of Ortho Pharma and Olson 1988 also render each of claims 1-6, 8-23, 25 and 27-28 obvious; 3) The addition of Widder to Ortho Pharma and Olson 1988 renders each of claims 7, 24, and 26 obvious.

VIII. TECHNICAL BACKGROUND

42. As described below, it is my opinion that the '432 patent was not the first to teach: (1) the role of vitamin A in the eye and vision; (2) the role of natural vitamin A byproducts in the pathophysiology of macular degeneration, including Stargardt disease; (3) that administration of vitamin A is useful for the treatment of eye diseases, including macular degeneration; (4) that deuterated vitamin A had been formulated in a pharmaceutically acceptable carrier for administration to

humans in a safe manner for decades; (5) that deuterated compounds were a known means for slowing undesirable reactions in vivo; and (6) synthesis of the claimed C₂₀-deuterated vitamin A.

43. As I discuss in detail below, and relying on the opinions of Dr. Guengerich where appropriate, it was known as of the priority date that (i) it was desirable for patients with macular degeneration to have ample supplies of vitamin A to feed the visual cycle; (ii) it was desirable to inhibit the formation of macular degeneration-associated lipofuscin that was created as a harmful byproduct of the visual cycle without, if possible, interfering with the visual cycle; (iii) deprotonation of carbon 20 of ATR (all-trans-retinal, also known as all-*trans*-retinaldehyde), an important form of Vitamin A, was a prerequisite for formation of carotenoid waste products such as A2E (also known as *N*-retinylidene-*N*-retinylethanolamine) and ATR dimer, which constitute important components of lipofuscin; (iv) C₂₀-deuterated vitamin A had been described in the art; (v) deuterated vitamin A had been formulated in pharmaceutically acceptable carriers for safe administration to humans in a safe manner for decades; (vi) deuteration of an existing compound was a known method of creating improved compounds. As such, a person of ordinary skill in the art had good reason to formulate C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier and to administer the

same to reduce the accumulation of lipofuscin, a toxic byproduct of vitamin A in the visual cycle, in order to treat macular degeneration.

A. It Was Known that Vitamin A Plays a Major Ocular Role.

44. From the perspective of a clinician, by 2007 it was well understood that vitamin A played an essential role in vision and ocular health. Vitamin A “is a generic term for a variety of related compounds, including retinol, retinyl palmitate, retinoic acid and the pro-vitamin A carotenoids,” with the “most active provitamin A carotenoids” being all-*trans*-beta-carotene, which is also referred to as beta-carotene. EX1025 (McCullough), 289. Retinal (also known as retinaldehyde) and retinol acetate (also known as retinyl acetate) are two additional examples of common, natural forms of vitamin A. *See, e.g.*, EX1002, ¶54 (Dr. Guengerich’s declaration).

45. Vitamin A compounds were known to be essential to eye health due to, among other things, their important role in the “visual cycle.” In fact, the visual cycle was often even referred to as the “retinoid cycle,” since Vitamin A’s role in the visual cycle was so prominent and essential. EX1009 (Widder), 1:12-16. Inventors Kenneth Widder, Jay Lichter, and Nathan L. Mata published a patent application entitled “Methods and Compositions for Treating Ophthalmic Conditions via Serum Retinol, Serum Retinol Binding Protein (RBP), and/or Serum Retinol-RBP Modulation.” The patent application was published on January

19, 2006, with a publication number of WO 2006/007314 A1. I will refer to this patent application as Widder.

46. Vitamin A compounds are retinoids and include vitamin A in the form of an alcohol, aldehyde, acid, or ester. *See* EX1026 (Olson 1964), 281 (“Retinol, retinal, and retinoic acid are used for vitamin A alcohol, vitamin A aldehyde, and vitamin A acid, respectively.”), 288 (“Retinol in foodstuffs and in tissues appears largely in the form of its ester, and to some extent as the free alcohol.”). Pro-vitamin A carotenoids were also well-known, including common nutrients such as beta-carotene. EX1026 (Olson 1964), 281. Olson 1964 was an article entitled “The biosynthesis and metabolism of carotenoids and retinol (vitamin A)” that was published in volume 5 of the periodical publication *Journal of Lipid Research* in 1964. Beta-carotene was known to be readily obtainable from carrots and other vegetables and fruits. Beta-carotene is absorbed in the small intestine and converted in the small intestine into retinal (retinaldehyde) by the enzyme beta-carotene dioxygenase. EX1058 (Duszka), 2550. 2550. Duszka was an article entitled “Rat Intestinal β -Carotene Dioxygenase Activity Is Located Primarily in the Cytosol of Mature Jejunal Enterocytes” that was published in volume 126 of the periodical publication *Journal of Nutrition* in 1996.

47. Widder describes the important role of vitamin A in the visual cycle. EX1009 (Widder), 1:12-16. The visual cycle is critical for sight and involves

enzymatic reactions that occur in the retinal pigment epithelium (RPE) and in the outer segment of the rods within the eye. For example, Widder states:

The *visual cycle or retinoid cycle* is a series of light-driven enzyme catalyzed reactions in which the active visual chromophore rhodopsin is converted to an all-trans-isomer that is then subsequently regenerated. Part of the cycle occurs within the outer segment of the rods and part of the *cycle occurs in the retinal pigment epithelium (RPE)*. Components of this cycle include various dehydrogenases and isomerases, as well as proteins for transporting intermediates between the photoreceptors and the RPE.

EX1009 (Widder), 1:12-16. RPE cells provide multiple functions within the eye, and their role in the visual cycle was understood to be critical for sight. As a further example, Lucian V. Del Priore; Ya-Hui Kuo, and Tongalp H. Tezel published an article entitled “Age-Related Changes in Human RPE Cell Density and Apoptosis Proportion In Situ” in the periodical *Investigative Ophthalmology & Visual Science* in 2002. I will refer to this article as Del Priore. Del Priore states:

The RPE has many physiological functions, including maintenance of the blood–outer retinal barrier, phagocytosis, recycling of the tips of the photoreceptor outer segments, and isomerization of visual pigments....Dysfunction of the RPE may play a role in the pathogenesis of a

wide variety of sight-threatening diseases, including age-related macular degeneration (AMD).

EX1027 (Del Priore), 3312.

48. A person of ordinary skill in the art would have been well aware that sufficient ocular concentrations of vitamin A were not only important to support vision through the visual cycle but also were important to other aspects of ocular health. For example, George Wolf published an article entitled “A History of Vitamin A and Retinoids” on July 1, 1996, in volume 10 of the periodical publication the *FASEB Journal*. As explained by Wolf, et al., “Vitamin A deficiency can affect two parts of the eye: the epithelial covering (cornea and conjunctiva) and the retina (rhodopsin and iodopsin).” EX1028 (Wolf), 2.

49. As another example, McCullough et al. published an article entitled “The effect of vitamin A on epithelial integrity” in 1999 in volume 58 of the periodical publication *Proceedings of the Nutrition Society*. I will refer to this article as McCullough. McCullough explained that vitamin A deficiency causes undesirable disorders in the eye, including visual disturbances, night blindness, conjunctival xerosis, Bitot’s spots, corneal ulceration, corneal scarring, and xerophthalmia fundus. EX1025 (McCullough), 290. McCullough explained that even “marginal Vitamin A status clearly impairs the integrity of epithelial tissues. These effects are more clearly seen in the eye....” EX1025 (McCullough), 292.

50. As another example, Alfred Sommer published an article entitled “Effects of Vitamin A Deficiency on the Ocular Surface” in June 1983 in volume 90 of the periodical publication *Ophthalmology*. I will refer to this article as Sommer. Sommer explains that “[v]itamin A deficiency is one of the most common causes of ocular surface abnormalities and blindness....At least five million African and Asian children develop clinically significant vitamin A deficiency every year of whom a quarter million go blind.” EX1029 (Sommer), 592. Sommer also explains that “[v]itamin A is required for normal differentiation of mucus-secreting epithelia....In vitamin A deficiency mucosal epithelium of a wide variety of organs undergoes keratinizing metaplasia....The eye is but the most obvious and dramatic example.” EX1029 (Sommer), 592.

51. As another example, Colin Kemp and co-authors published an article entitled “Visual Function and Rhodopsin Levels in Humans with Vitamin A Deficiency” in 1988 in Volume 46 of the periodical publication *Experimental Eye Research*. I will refer to this article as Kemp (EX1054). Kemp found that patients complaining of night blindness who had Vitamin A deficiency secondary to gastrointestinal malabsorption had reduced retinal cone adaptation and no measurable rod function. Administration of Vitamin A supplements restored night vision and rod and cone function to normal within eight days. Rhodopsin regeneration also improved after Vitamin A supplementation. EX1054 (Kemp),

185. Accordingly, a person of ordinary skill in the art considering an ophthalmic treatment strategy involving ocular levels of vitamin A levels would have desired to maintain sufficient vitamin A levels in the eye both to support the visual cycle as well as to maintain the integrity of ocular tissues.

B. Lipofuscin, An Undesirable Vitamin A Byproduct of the Visual Cycle, Was Understood to Contribute to Macular Degeneration.

52. By 2007, a person of ordinary skill in the art would have understood that the use of vitamin A in the visual cycle led to accumulation of an undesirable byproduct called lipofuscin that was involved in the pathophysiology of macular degeneration. Accordingly, persons of ordinary skill sought to treat macular degeneration by finding ways to decrease the amount of lipofuscin accumulation in the retina and RPE.

53. For example, Roxana A. Radu et al. published an article entitled “Reductions in in Serum Vitamin A Arrest Accumulation of Toxic Retinal Fluorophores: A Potential Therapy for Treatment of Lipofuscin-Based Retinal Diseases” in volume 46 of the periodical publication *Investigative Ophthalmology & Visual Science* in 2005. I will refer to this article as Radu 2005. Radu 2005 states “[l]ipofuscin arises in the RPE from incomplete digestion of these retinaldehyde-rich outer-segment fragments....The major fluorophore of lipofuscin is the bis-retinoid, N-retinylidene-N-retinylethanolamine [also known as A2E]....Dramatic accumulation of A2E has been observed in the RPE of ABCA4

knockout mice, which represent an animal model for *ABCA4*-mediated macular and retinal degenerations.” EX1030 (Radu 2005), 4393. Radu 2005 further states that “[t]he much faster accumulation of A2E in the above-described mouse models and humans with several forms of macular and retinal degeneration results in compromised RPE function and ultimately blindness due to photoreceptor death. Thus, the targeting of A2E accumulation in RPE cells appears a reasonable therapeutic strategy to slow the progression of visual loss in these patients.” EX1030 (Radu 2005), 4393.

54. As another example, Janet R. Sparrow et al., published an article entitled “A2E, a byproduct of the visual cycle” in volume 43 of the published periodical *Vision Research* in 2003. I will refer to this article as Sparrow. Sparrow explains that lipofuscin pigment A2E is formed as a “consequence of light-related vitamin A recycling” within the visual cycle and that lipofuscin toxicity is associated with the development of macular degeneration. EX1033 (Sparrow), Abstract. Sparrow notes that “life-time accumulations of lipofuscin can, under some circumstances, reach levels that provoke RPE atrophy...[suggesting] that the light capturing function of the retina underlies mechanisms leading to macular degeneration.” EX1033 (Sparrow), 2987.

55. As another example, George Wolf published an article entitled “Lipofuscin and Macular Degeneration” in volume 61 of the published periodical

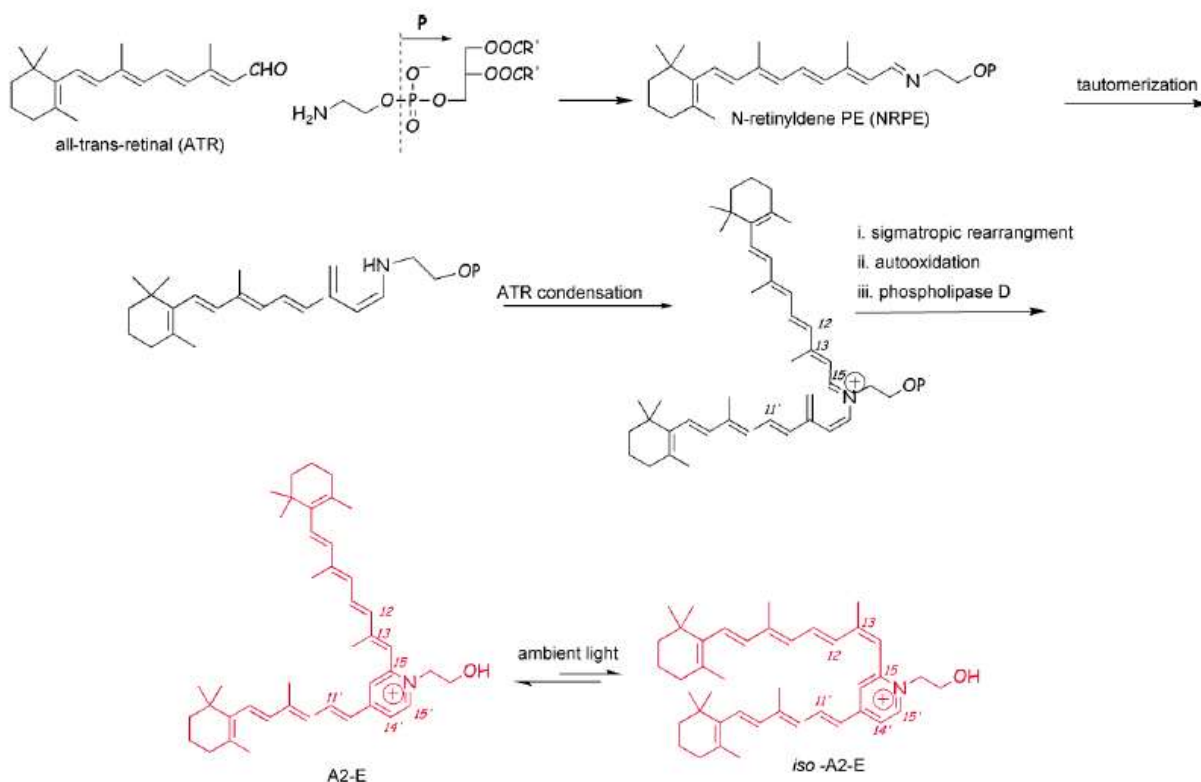
Nutrition Review in 2003. I will refer to this article as Wolf 2003. Wolf 2003 explains that lipofuscin is a by-product of the light cycle, and that “A2E strongly absorbs blue light and initiates apoptosis in cultured human RPE cells loaded with A2E....An intact RPE is indispensable for survival of rods and cones. Thus, AMD can be traced to increased accumulation of A2E in the RPE.” EX1034 (Wolf 2003), 343.

56. Other references similarly recognized that A2E contributes to macular degeneration by inducing RPE cell apoptosis. For example, Stargardt disease is an eye disease most commonly caused by a mutation in the gene coding for the ATP-binding cassette (ABC) transporter ABCR (also referred to as ABCR4 in some publications). This genetic mutation leads to the accumulation of A2E in RPE cells and causes macular degeneration and loss of vision. EX1034 (Wolf 2003).

Studying the effects of Stargardt’s disease, Roxana Radu et al. published an article entitled “Treatment with isotretinoin inhibits lipofuscin accumulation in a mouse model of recessive Stargardt’s macular degeneration” in volume 100 of the periodical *Proceedings of the National Academy of Sciences of the United States of America*. I will refer to this article as Radu. Radu explains that the “primary pathologic defect in Stargardt’s disease is the accumulation of toxic lipofuscin pigments such as N-retinylidene-N-retinylethanolamine (A2E) in cells of the retinal pigment epithelium.” EX1035 (Radu), Abstract. Sparrow further illustrates

the connection between Stargardt disease and lipofuscin accumulation, stating that Stargardt disease is “characterized by copious accumulation of RPE lipofuscin.” EX1033 (Sparrow), 2984.

57. As another example, Nathan Fishkin et al. published an article entitled “A2-Rhodopsin: a new fluorophore isolated from photoreceptor outer segments” in the periodical Organic & Biomolecular Chemistry in 2003. EX1036 (Fishkin 2003). I will refer to this article as Fishkin 2003. Fishkin described that vitamin A cycling in the retina causes A2E deposition in RPE cells. EX1036 (Fishkin 2003), 1011 (stating that “[a]s a consequence of the continual light-related vitamin A cycling in the retina, the orange-emitting fluorophore A2E (Fig. 1) is deposited in retinal pigment epithelial (RPE) cells as a constituent of the fluorescent pigments and uncharacterized lipids and proteins that constitute lipofuscin”). I have reproduced Fig. 1 of Fishkin 2003 below, which shows the biosynthesis of A2E from all-*trans* retinal (ATR) and phosphatidylethanolamine:



58. Fishkin 2003 explains that “Phagocytosis of outer segment disk membrane causes A2E to be deposited in RPE cells. As with other lipofuscin components, A2E cannot be degraded by RPE lysosomal enzymes, and thus accumulates.” EX1036 (Fishkin 2003), 1102. Fishkin 2003 further describes that A2E is present in the RPE of patients with Stargardt disease and that the “the demise of these [RPE] cells in some retinal disorders, such as AMD and Stargardt disease, is a critical component of the disease process.” EX1036 (Fishkin 2003), 1101.

59. As explained in Dr. Guengerich’s declaration (EX1002), Mata (EX1010, discussed in more detail below) explicitly discloses that deprotonation of

carbon 20 of retinal is required for formation of A2E/lipofuscin. EX1002, ¶¶44-46; see Section X.E below. Dr. Guengerich explains that the deprotonation of C-20 would have been recognized as the rate-limiting step in A2E formation. EX1002, ¶93.

60. Given the recognition that lipofuscin containing A2E contributes to macular degeneration by inducing RPE cell apoptosis, various methods were employed to reduce lipofuscin formation and accumulation in the retina and/or RPE. One method was to counteract the apoptosis of RPE cells by administering negatively-charged phospholipids. EX1009 (Widder), 6:7-8. For example, Widder discloses that “[t]he use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies” and that “[e]xamples of suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include *cardiolipin* and *phosphatidylglycerol*.” EX1009 (Widder), 33:1-7 (citing Shaban and Richter, EX1020; and Shaban, EX1021).

61. Hamdy Shaban and Christoph Richter published an article entitled “A2E and Blue Light in the Retina: The Paradigm of Age-Related Macular Degeneration” in volume 383 of the published periodical *Journal of Biological Chemistry* in 2002. This article will be referred to as Shaban and Richter (EX1020). Shaban and Richter is a review article describing mechanisms by which

retinal photoreceptors may be damaged by light, especially blue light, resulting in cell death and the development of AMD. EX1020, Abstract. Shaban and Richter observe that it was generally believed that the accumulation of lipofuscin in RPE cell phagolysosomes was a predictor of AMD. EX1020, 537.

62. Shaban et al published an article entitled “Phosphatidylglycerol Potently Protects Human Retinal Pigment Epithelial Cells Against Apoptosis Induced by A2E, a Compound Suspected to Cause Age-related Macula Degeneration” in 2002 in the published periodical *Experimental Eye Research*. This article will be referred to as Shaban et al. (EX1021). Shaban et al. teaches that certain negatively-charged phospholipids are useful for ameliorating existing lipofuscin components (e.g., A2E). EX1021, Abstract.

63. These two references, cited by Widder, explain that these negatively-charged phospholipids counteract the RPE cell apoptosis induced by A2E, EX1020 (Shaban & Richter), Abstract (“[f]ree retinal...is phototoxic, and is a precursor of the (photo)toxic compound A2E, which...induces cell death by apoptosis. Cell death induced by A2E in the dark is prevented by negatively charged phospholipids.”); EX1021 (Shaban et al.), Abstract (“A2E at low concentrations causes apoptosis in cultured human retinal pigment epithelial cells....Phosphatidylglycerol, a negatively charged phospholipid and immediate biosynthetic precursor of cardiolipin readily inhibits apoptosis.”). Thus, the Shaban

& Richter and Shaban et al. articles cited by Widder demonstrate an understanding that administration of these phospholipids to the eye could be useful in treating macular degeneration associated with lipofuscin-induced RPE cell death (apoptosis).

64. Another approach attempted was to control the concentration in the eye of the vitamin A used in the visual cycle that is responsible for lipofuscin formation. As I explained above, the visual cycle involves converting Vitamin A from its alcohol form (retinol) ultimately into an aldehyde form (retinal). It is the all-trans aldehyde form that results in the undesirable A2E byproduct.

Accordingly, practitioners studied various ways of inhibiting the A2E biosynthesis pathway at its source (i.e., reducing all-trans-retinal concentrations in the eye).

65. For example, Wolf 2003 explains, *inter alia*, that if “light-induced formation of all-*trans*-retinal is slow, it will not accumulate but rather will be reduced to all-*trans*-retinol. All-*trans*-retinal then proceeds through the visual cycle...and will not be available for A2E formation.” EX1034 (Wolf 2003), 342.

Wolf 2003 thus employed isotretinoin to prevent the accumulation of A2E by slowing down the visual cycle. EX1034 (Wolf 2003), Abstract. Wolf 2003 suggests reducing lipofuscin formation “to prevent macular degeneration” and explained that isotretinoin proved effective as a chemopreventive drug for Stargardt disease, which is a particular form of retinal dystrophy characterized by

degeneration of the macula. EX1034 (Wolf 2023), 343 & 345 (“[t]his work represents the first proven chemopreventive drug for Stargardt disease, at least in an animal model.... Isotretinoin might also be used as a chemopreventive drug for AMD.”).

66. As another example, the prior art taught the use of agents, such as fenretinide (also known as HPR or 4-HPR), for decreasing the amount of retinol binding protein (RBP) and preventing A2E formation. EX1009 (Widder), 42:16-19; 45:21-34; 51:4-16. Importantly, it was known that delivery of retinol to relevant structures within the eye is dependent upon RBP. EX1030 (Radu 2005), 4394 (stating that “HPR [(fenretinide)] exerts its effect on retinol levels by competing for binding sites on RBP....[T]he uptake of retinol by the eye is largely dependent on delivery by RBP.”). Administering fenretinide thus was understood to reduce lipofuscin formation by decreasing the concentration of vitamin A entering relevant structures within the eye. Radu and coauthors concluded that “It is apparent from these data that a direct effect of HPR on RBP, rather than inhibition of the visual cycle, is the principal mechanism of HPR action. These findings support therapeutic efficacy for HPR to reduce accumulation of lipofuscin fluorophores and illustrate the dependence of A2E biosynthesis on serum retinol levels.” EX1030 (Radu 2005), 4399.

67. For any of these approaches to reducing lipofuscin formation that involve reducing vitamin A concentrations in the eye or slowing the visual cycle, there were recognized downsides that weighed against the benefits of reducing lipofuscin formation. For example, Wing C. Law and Robert R. Rando published an article entitled “The Molecular Basis of Retinoic Acid Induced Night Blindness” in volume 161 of the periodical publication “Biochemical and Biophysical Research Communications” on June 15, 1989. I will refer to this article as Law. As explained by Dr. Law, inhibiting the visual cycle can lead to deleterious visual effects. EX1037 (Law), 825 (stating that “[d]rugs which inhibit enzymes of the classical visual cycle...would also be expected to produce night blindness and other ocular disorders, since they reduce the flow of retinoids through the system and hence reduce the production of the visual chromophore 11-*cis*-retinal.”). Law further describes that the retinoids all-*trans*- and 13-*cis*-retinoic acid inhibit enzymes in the visual cycle, and would be expected to lead to night blindness. EX1037 (Law), 825-826 (stating that “all-*trans* and 13-*cis*-retinoic acids... appear to powerfully inhibit the ocular retinol dehydrogenases, thus hindering the formation of 11-cis-retinal from its 11-cis-retinol precursor. This inhibition...would be expected to lead to night blindness.”).

68. Radu 2005 also identifies impairment of the visual cycle as a downside of these approaches. Radu notes that “Clinically, investigators noted

reductions in serum retinol, RBP, and delayed dark adaptation [in patients treated with HPR (fenretinide)]. Subsequent investigations showed a high correlation between HPR-induced reductions in serum RBP-retinol levels and manifestation of delayed dark adaptation.” EX1030 (Radu), 2005, 4399. Their experimental data were in accordance with these clinical observations: “HPR-treated mice demonstrated a delay in return of the rod photoresponse to the dark-adapted baseline levels after a 30-second photobleach...” EX1030 (Radu 2005), 4397.

69. Additionally, both Radu and Sieving also demonstrate that slowing the visual cycle produces adverse effects. EX1035 (Radu), 4747 (stating that isotretinoin “treatment was associated with delayed dark adaption”); EX1038 (Sieving), Abstract (“[E]ven a single dose of isotretinoin slowed the recovery of rod signaling after exposure to an intense bleaching light, and... rhodopsin regeneration was markedly slowed.”).

70. As such, there were good reasons for persons of ordinary skill in the art by 2007 to identify ways to inhibit the lipofuscin biosynthesis pathway downstream of the vitamin A retinoids involved in the visual cycle, in order to avoid impairing the visual cycle.

C. Macular Degeneration Was a Major Cause of Blindness and Was Conventionally Treated with Vitamin A.

71. By 2007, age-related macular degeneration was understood to be a major cause of blindness. For example, an article entitled “Age related macular

degeneration” by Amresh Chopdar and co-authors was published on March 1, 2003, in volume 326 of the periodical publication *British Medical Journal*.

Chopdar et al. state that “[a]ge related macular degeneration is already the leading cause of blindness in the Western world. Between 20 and 25 million people are affected worldwide, a figure that will triple with the increase in the ageing population in the next 30-40 years.” EX1039 (Chopdar), 485. Age-related macular degeneration was commonly diagnosed based on fundus examination and imaging, including fundus photography and angiography, with common symptoms including gradual or sudden loss of vision, blurred vision, and/or metamorphopsia (where the shape of objects appears distorted). EX1039 (Chopdar), 486. Optical coherence tomography (OCT) imaging was also widely used for diagnosis of AMD as of the priority date.

72. Two major forms of age-related macular degeneration exist, the non-exudative (“dry”) and exudative (“wet”) forms. Angiography with fluorescein and sometimes indocyanine green was historically used to both confirm the presence of macular degeneration and to determine which form was present. For example, Chopdar states that “In addition to assessment of visual acuity and a full ophthalmological examination, exudative age-related macular degeneration is usually investigated by retinal and choroidal angiography using fluorescein and indocyanine green dyes.” EX1039 (Chopdar), 486. In the non-exudative form of

the disease, subjects often experience a gradual decline in visual acuity, whereas in the exudative form fluid may rapidly accumulate in or under the retina, often causing a rapid reduction in visual acuity. In the exudative form, “neovascular complexes” grow into the sub-RPE, subretinal and/or intraretinal spaces and leak fluid or blood, “leading to oedema (extravasation of blood and lipid materials), which progressively disrupts visual function.” EX1039 (Chopdar), 486. Chopdar explains that “[t]he main symptom of non-exudative age-related macular degeneration is a gradual increase in difficulty of fine discriminate tasks; the main symptoms of the exudative form are central blurring and distortion of sudden onset.” EX1039 (Chopdar), 485.

73. Treatments available for exudative macular degeneration as of the priority date included laser photocoagulation, photodynamic therapy, and intravitreal injections of pharmaceuticals (such as pegaptanib, ranibizumab and bevacizumab) targeting vascular endothelial growth factor (VEGF). EX1039 (Chopdar), 487. Rosenfeld, P.J. et al., “Ranibizumab for Neovascular Age-Related Macular Degeneration”, 355 New England Journal of Medicine, 1419-31 (October 5, 2006), EX1055. Furthermore, it was well known to ophthalmologists as of the priority date that nutrition plays an important role in macular degeneration, and that the risk of AMD progression, and particularly the risk of transition from dry AMD to wet AMD, was significantly reduced in non-smoking patients with

moderate dry AMD who were given beta-carotene, in combination with vitamins C and E as well as zinc and copper. EX1039 (Chopdar), 487.

74. By 2007, administering beta-carotene (a pro-vitamin A carotenoid) to patients with atrophic macular degeneration, together with Vitamins C and E and zinc and copper, was considered by most ophthalmologists to be the standard of care for reducing the risk of wet AMD in patients with intermediate to severe dry AMD. This was due in large part to a series of ground-breaking publications by the Age-Related Eye Disease Study (AREDS) Research Group. For example, the AREDS Research Group published “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” in the periodical *Archives of Ophthalmology* in 2001. For the sake of brevity, I will refer to this study as AREDS.

75. AREDS was a well-known set of clinical trials that researched the effects of vitamin C (ascorbic acid), vitamin E (*dl*-alpha tocopheryl acetate), vitamin A (beta-carotene), zinc (zinc oxide) and copper (cupric oxide) in subjects with dry age-related macular degeneration. EX1022 (AREDS), Abstract, 14. AREDS reported that “antioxidants [in the form of vitamins C and E and beta carotene, a pro-vitamin form of vitamin A,] plus zinc and copper significantly reduced the odds of developing advanced AMD.” EX1022 (AREDS), Abstract.

AREDS further disclosed that there was an “apparent treatment benefit” of vitamins C, E, and A plus zinc and copper “for each of the events predefined in the study protocol to be signs of advanced AMD....” EX1022 (AREDS), 9. In view of the results of AREDS, it became common practice by 2007 to administer beta-carotene to patients with non-exudative or atrophic macular degeneration (except in tobacco smokers, in whom beta-carotene had been shown to increase the risk of lung cancer), together with Vitamins C and E, and minerals including zinc and copper.

76. By 2007, it was taught in the literature that the administration of Vitamin A was beneficial for treating eye diseases more generally. For example, Eliot L. Berson, Bernard Rosner, Michael A. Sandberg, K. C. Hayes, Britain W. Nicholson, Carol Weigel-DiFranco, and Walter Willett published an article entitled “A Randomized Trial of Vitamin A and Vitamin E Supplementation for Retinitis Pigmentosa” in the periodical publication *Archives of Ophthalmology* volume 111, in 1993. This article is referred to as “Berson.” Berson teaches that vitamin A slowed eye disease progression, such as in retinitis pigmentosa (a retinal dystrophy), by slowing the rate of retinal functional decline. EX1040 (Berson), Abstract (stating that “[T]he two groups receiving 15,000 IU/d of vitamin A had on average a slower rate of decline of retinal function than the two groups not receiving this dosage...”). As another example, Samuel G. Jacobson and co-

authors published an article entitled “Night blindness in Sorsby’s fundus dystrophy reversed by Vitamin A” in the periodical publication *Nature Genetics* volume 11, in 1995. This article is referred to as Jacobson. Jacobsen teaches rapid resolution of night blindness after administration of Vitamin A to subjects suffering from early forms of Sorsby’s fundus dystrophy, a retinal degeneration. EX1041 (Jacobson), Abstract (“Within a week [of oral Vitamin A supplementation], the night blindness disappeared in patients at early stages of disease.”). Similarly, Alfred Sommer and co-authors, in an article entitled “Oral Versus Intramuscular Vitamin A in the Treatment of Xerophthalmia” in Volume 8168 (Part 1) of the journal *Lancet* published on March 15, 1980, demonstrated that very high doses of Vitamin A (100,000 IU to 200,000 IU) could safely be administered orally or intramuscularly to children for effective treatment of the eye disease xerophthalmia caused by Vitamin A deficiency. EX1056.

77. By 2007, it was well understood that chronic administration of vitamin A to patients was also safe for treatment of non-ocular problems. For example, David Alberts et al., published an article entitled “Safety and Efficacy of Dose-Intensive Oral Vitamin A in Subjects with Sun-Damaged Skin” in the periodical *Clinical Cancer Research* in year 2004. Alberts et al. explains that vitamin A was administered to people for extended periods of time and was

determined to be safe. EX1042 (Alberts), Abstract (stating that “vitamin A doses of 50,000 and 75,000 IU/day for one year proved safe....”).

78. As another example, an article by David A. Ross, entitled “Recommendations for Vitamin A Supplementation,” (EX1043, “Ross”) was published in Volume 132 of the Journal of Nutrition in 2002. Ross states that “[t]he efficacy of vitamin A supplementation of young children is one of the best-proven, safest and most cost-effective interventions in international public health.” EX1043 (Ross), Abstract. Ross further states that “International Vitamin A Consultative Group (IVAG) also recommends that three 50,000-international unit (IU) doses of vitamin A should be given at the same time as infant vaccines during the first 6 months of life). Noting that Vitamin A supplementation not only treats and prevents xerophthalmia but also reduces the risk of infections and even death in patients with Vitamin A deficiency, Ross thus provides an example of literature reflecting then-existing practices of administering large doses of vitamin A even to vulnerable populations.

79. As such, Vitamin A was routinely administered before the critical date to humans, including for treating eye disorders, and a person of ordinary skill in the art had a good reason to administer Vitamin A retinoids to prevent or treat disorders or diseases of the eye.

D. Deuterated Forms of Vitamin a Had Been Safely Administered to Humans for Decades in Pharmaceutically Acceptable Carriers.

80. By 2007, it was well known that formulations containing deuterated vitamin A in a pharmaceutically acceptable carrier had been administered for diagnostic purposes to humans for decades without incident. For example, Judy Ribaya-Mercado et al., published an article entitled “Dietary vitamin A intakes of Filipino elders with adequate or low liver vitamin A concentrations as assessed by the deuterated-retinol-dilution method: implications for dietary requirements” in the periodical American Journal of Clinical Nutrition in 2004. Judy Ribaya-Mercado et al. studied vitamin A levels in elderly patients by administering deuterated vitamin A in corn oil, a pharmaceutically acceptable carrier. EX1053 (Ribaya-Mercado), 634 (capsules containing 0.015 mmol of tetradeuterated retinyl acetate (all-trans-retinyl-10,19,19,19-[²H₄]acetate) in corn oil were ingested by subjects).

81. As another example of administration of deuterated vitamin A to humans, Haskell et al., published an article entitled “Use of the deuterated-retinol-dilution technique to assess total-body vitamin A stores of adult volunteers consuming different amounts of vitamin” in the periodical The American Journal of Clinical Nutrition in 1999. Haskell et al., describe the use of the “deuterated-retinol-dilution (DRD) technique” for estimating total body storage of vitamin A. EX1044 (Haskell), Abstract. The DRD technique was utilized by administering

deuterated retinyl acetate to human subjects. EX1044 (Haskell), Abstract (“Two oral doses of [$^2\text{H}_4$]-retinyl acetate [52.4 mmol retinol equivalent (RE)] were administered to... 26 men... during a 75- or 129-d period.”). Haskell administered vitamin A in corn oil. EX1044 (Haskell), 875.

82. As a further example, an article entitled “Vitamin A concentrations in liver determined by isotope dilution assay with tetradeuterated vitamin A and by biopsy in generally healthy adult humans” was published in 1989 by Harold C Furr, Olivier Amedee-Manesme, Andrew J Clifford, H Robert Bergen III, A Daniel Jones, Dale P Anderson, and James A Olson in the periodical publication The American Journal of Clinical Nutrition. This is the same Olson research group that published Olson 1988, and shares many of the same authors. This article will be referred to as Olson 1989.

83. Olson 1989 administered a composition comprising 45 mg doses of tetradeuterated retinyl acetate in corn oil to eleven subjects in order to study vitamin A status in the subjects. EX1007 (Olson 1989), 713, 714. Olson 1989 taught that administration of the deuterated vitamin A analog was satisfactory, stating that the intervention was a “benign, relatively noninvasive procedure.” EX1007 (Olson 1989), Abstract.

84. Furthermore, Marjorie Haskell et al. published an article entitled “Assessment of vitamin A status by the deuterated-retinol dilution technique and

comparison with hepatic vitamin A concentration in Bangladeshi surgical patients” in volume 66 of the periodical publication *American Journal of Clinical Nutrition* in 1997. I will refer to this article as Haskell 1997. Haskell 1997 studied vitamin A levels in thirty-one subjects with the use of the deuterated-retinol-dilution (DRD) technique. EX1045 (Haskell 1997), 67. In particular, Haskell 1997 studied vitamin A stores by administering a composition comprising a dose of 0.753 $\mu\text{mol/kg}$ body weight of [$^2\text{H}_4$]-retinyl acetate in corn oil. EX1045 (Haskell 1997), Abstract, 67.

85. Therefore, by 2007 a person of ordinary skill in the art would have understood that it was well within the skill in the art to formulate deuterated vitamin A in a pharmaceutically acceptable carrier, including for administration to human subjects.

86. Moreover, in none of these studies was there any report of any adverse event attributed to the deuteration of the vitamin A. And as Dr. Guengerich explains, none of carbons 10, 19, or 20 of vitamin A were understood to play a role in the reactions required for the visual cycle. EX1002, ¶55.

E. There Was Significant Interest in Deuterated Versions of Known Therapeutics to Slow Rates of Undesired Reactions.

87. A person of ordinary skill in the art before 2007 would have understood that there was significant interest in making deuterated versions of known therapeutics in order to slow rates of undesirable reactions. For example,

D.J. Kushner and A. Baker published an article entitled “Pharmacological uses and perspectives of heavy water and deuterated compounds” in the periodical *Canadian Journal of Physiology and Pharmacology* in 1999. I will refer to this article as Kushner. Kushner explains that deuterated drugs and their actions are more easily understood and a less complex subject than use of deuterium oxide. EX1046 (Kushner), 85 (The use of deuterated drugs “in studies of drug metabolism is very well established, as is their contribution to studies of other biochemical pathways....The continuing need for...deuterated compounds in general, in physiological, pharmacological, and biochemical studies, cannot be questioned. ”).

88. Kushner describes that a multitude of deuterated pharmaceutical compounds can be made. EX1046 (Kushner), 85 (explaining that deuterated version of camptothecin, nordiazepam, diazepam, Deuterated amines, nonsteroidal anti-inflammatory 2-arylpropionic acids, the mucolytic drug domiodol, anti-tumor agents, psychoactive drugs, and anti-malarial drugs have been prepared and that the list provided was “by no means exhaustive, and only suggests the range of substances studied”).

89. Kushner further discusses the safety of deuterated compounds, which are not radioactive (in contrast to tritiated compounds). For example, Kushner states that “past experience has shown how safe D₂O and deuterated compounds are...” and that deuterated compounds are widely used in studies because of their

low toxicity. EX1046 (Kushner), 83 (stating that deuterated compounds “are very widely used in studies of metabolism and movement of drugs and toxic substances in humans and other animals” in part because of “the very low toxicity of deuterated compounds”), 85 (stating that “[b]ecause of these considerations, and the very low toxicity of deuterated compounds (especially compared with radioactive ones) such drugs, as well as D₂O, are very widely used in studies of metabolism and movement of drugs and toxic substances in humans and other animals.”). Accordingly, there was significant interest before 2007 in making and formulating deuterated versions of known therapeutics and diagnostic compounds.

90. Additionally, by 2007, it was known that the deuteration of a compound was useful to slow the rate of an undesirable reaction involving the compound. *See, e.g.*, EX1046 (Kushner). Kushner explains that deuterated compounds generally can lower the production of toxic metabolites while also retaining their pharmacological properties. EX1046 (Kushner), 84 (“[t]he metabolic products of many drugs are toxic, and deuteration can lower such toxicity by reducing metabolism”).

91. To explain the reduction in reaction rates experienced by deuterated compounds, Blake et al., published an article entitled “Studies with Deuterated Drugs” in the periodical *Journal of Pharmaceutical Sciences* in 1975. I will refer to this article as Blake. Blake explained that deuterium is a stable heavy isotope of

hydrogen with twice the mass of regular hydrogen. EX1047 (Blake), 368. The increased mass results in increased stability of bonds involving deuterium, which can markedly slow the rates of reactions in deuterated compounds compared to their protium analogs. *Id.* (stating that “[t]he more stable deuterium bond requires a greater energy of activation...as a consequence, the rate of reaction involving a bond to deuterium is generally slower than that involving a bond to hydrogen. Thus, substitution of deuterium for hydrogen in a chemical bond can affect significantly the rate of bond cleavage and exert marked effects on the relative rates of chemical reactions.”).

92. The difference in reaction rates is referred to as the “kinetic isotope effect,” and the difference is most apparent when the breaking of the “C-H or C-D bond is involved in the rate-determining step [where D = deuterium].” *Id.* In particular, Blake explains that a large isotope effect is “**apparent where cleavage involves a bond to deuterium at the reaction site.**” *Id.* (emphasis added).

93. As a further example, Leslie McCarty et al., published an article entitled “The Effects of Deuteration on the Metabolism of Halogenated Anesthetics in the Rat” in the periodical *Anesthesiology* in 1979. Leslie McCarty et al. studied multiple deuterated compounds and their effect on metabolism. EX., EX1048 (McCarty), Abstract. After administering the compounds in animal studies, McCarty et al. concluded that deuteration of compounds predominantly

slowed their metabolism. EX1048 (McCarty), Abstract (stating that “deuteration of volatile anesthetics changes their metabolism, in most cases producing decreases in metabolism”).

F. C₂₀-Deuterated Retinoids Were Known

94. A person of ordinary skill in the art by 2007 would have been aware that C₂₀-deuterated vitamin A had been synthesized and purified. For example, an article entitled “Synthesis of Tri-, Tetra-, and Penta-Deuterated Forms of Vitamin A” was published by H. Robert Bergen, Harold C. Furr, and James A. Olson, researchers at Iowa State University Department of Biochemistry and Biophysics, in the periodical publication *Journal of Labelled Compounds and Radiopharmaceuticals* in 1988. I will refer to this article as Olson 1988.

95. As discussed below under Section X.A., Olson 1988 specifically discloses deuterated vitamin A compounds, including “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate,” and processes for their synthesis. EX1006 (Olson 1988), 11. In fact, Olson 1988 provides detailed instructions for making these deuterated vitamin A analogs, and discloses that deuterated vitamin A is useful for studying the metabolism of vitamin A. As such, C₂₀-deuterated retinoids were known before 2007.

IX. CLAIM CONSTRUCTION

96. I have been advised by Counsel that the claims should be understood according to their ordinary and customary meaning as 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. I have applied the plain and ordinary meaning of the claims in my analysis below.

X. SUMMARY OF ASSERTED REFERENCES

A. Olson 1988 (EX1006)

97. As I explained above, Olson 1988 published in the periodical publication the *Journal of Labelled Compounds and Radiopharmaceuticals* in 1988.

98. Olson 1988 discloses making deuterated vitamin A for use in biological studies. EX1006 (Olson 1988), 11 (stating that “[f]or studying the metabolism of vitamin A in humans, nonradioactive deuterated or ¹³C labeled compounds of high purity are desired”). Olson 1988 specifically discloses “20,20,20-trideutero, 14,20,20,20-tetradeutero, 12,14,20,20,20-pentadeutero, and 10,19,19,19-tetradeutero analogs of retinoic acid ethyl ester and retinyl acetate,” and processes for their synthesis. EX1006 (Olson 1988), 11.

99. Accordingly, a person of ordinary skill in the art would have understood that the prior art disclosed C₂₀-deuterated vitamin A and that deuterated

vitamin A compounds were desirable “[f]or studying the metabolism of vitamin A in humans.” EX1006, 11.

B. Olson 1989 (EX1007)

100. As I explained above, Olson 1989 published in the periodical publication *The American Journal of Clinical Nutrition* in 1989. Olson 1989 discloses a study estimating total body vitamin A reserves in humans by administering both non-deuterated vitamin A and deuterated vitamin A. For example, Olson 1989 discloses “The vitamin A status of 11 generally healthy surgical patients was estimated by measuring the dilution of a 45-mg oral dose of tetradeuterated retinyl acetate (99% pure).” EX1007 (Olson 1989), Abstract. Olson 1989 formulated the vitamin A in a pharmaceutically acceptable carrier (corn oil), regardless of whether or not the vitamin A was deuterated. EX1007 (Olson 1989), 714 (administering doses of “450 μ m retinyl acetate in corn oil and 45 mg of all-*trans* 10,19,19,19-[²H₄]retinol as retinyl acetate in corn oil”).

101. In the study, Olson 1989 describes that:

Eleven hospitalized patients (aged 22-87 y) scheduled for cholecystectomy (n= 6), gastroplasty (n= 4), and splenectomy (n= 1) were admitted into the study....[N]ine subjects routinely ingested normal amounts (900-2100 mg) of carotenoids and vitamin A....

EX1007 (Olson 1989), 713. Olson 1989 further describes previous studies that were conducted to verify the approach in humans and other animals (e.g., rats, sheep, and cattle), but notes that the previous human study did not verify the analysis of vitamin A levels by sampling of liver vitamin A in the subject.

EX1007 (Olson 1989), 713.

102. A person of ordinary skill in the art would understand that deuterated vitamin A had been safely administered to humans, including hospital patients and those with gastrointestinal disorders.

C. Ortho Pharma (EX1008)

103. A German patent application entitled “Carotenoid-containing product” was published in the Patent Gazette on January 18, 2007 with an application number of 20-2006-014-588.5. The published patent application is owned by Orthomol Pharmazeutische Vertriebs GmbH. For the sake of brevity, I will refer to this patent application publication as Ortho Pharma.

104. As I explained above in Section VIII.C, the standard of care by 2007 for treating age-related macular degeneration included the administration of vitamin A (in the form of the pro-vitamin A carotenoid beta-carotene), in combination with other vitamins, minerals, nutrients, and antioxidants to patients with moderate forms of dry (non-exudative) AMD. Ortho Pharma is a prior art publication that employs a particular implementation of this standard of care.

105. Ortho Pharma identifies several eye diseases, including macular degeneration, which it seeks to ameliorate by administering a product combining specified vitamins, minerals and nutrients. Ortho Pharma discusses the increased incidence of eye diseases, such as macular degenerations in general, and AMD in particular. For example, Ortho Pharma recites that “[i]t is well known that age-related eye diseases such as age-related macular degeneration or senile cataract have greatly increased and will continue to increase due to the rising average age of the population.” EX1008 (Ortho Pharma), ¶[0002], Abstract; Ortho Pharma asserts that its product is indicated for addressing an existing macular degeneration as well as counteracting the development of a macular degeneration. EX1008 (Ortho Pharma), ¶[0011] (showing “positive effects on the health of the eye in the case of an existing macular degeneration or senile cataract, as well as counteract a macular degeneration or senile cataract”).

106. Ortho Pharma’s implementation of treatment for macular degeneration envisions a product in which carotenoids, vitamins, flavonoids, and minerals are formulated in pharmaceutically acceptable carriers to provide dosage forms for use in the treatment of “age-related diseases such as age-related macular degeneration or senile cataract.” EX1008 (Ortho Pharma), ¶[0001]. Ortho Pharma sought to provide “a comprehensive supply of vitamins and minerals to the eye” in a way that “improves the absorption of the ingredients.” EX1008 (Ortho Pharma),

¶¶[0004], [0006]. Ortho Pharma sought to accomplish improved absorption by formulating some of the active ingredients in a solid dosage form and others in a liquid dosage form.

107. For example, Ortho Pharma discusses formulating vitamin A together with vitamins C, D₃, & E in combination with zinc in a liquid dosage form:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances: 50 mg to 500 mg of **vitamin C**; 0.1 mg to 2 mg of **vitamin A**; 10 mg to 400 mg of **vitamin E**; 0.2 mg to 5 mg of vitamin B₁; 0.2 mg to 5 mg of vitamin B₂; 5 mg to 50 mg of nicotinamide; 0.2 mg to 5 mg of vitamin B₆; 0.1 mg to 1 mg of folic acid; 5 µg to 50 µg of vitamin B₁₂; 0.1 µg to 10 µg of **vitamin D₃**; 50 µg to 300 µg of biotin; 3 mg to 30 mg of pantothenic acid; 2 mg to 30 mg of **zinc**; 20 µg to 100 µg of selenium; 20 µg to 100 µg of chromium; secondary plant compounds selected from the group comprising 6 mg to 32 mg of carotenoids comprising carotenoids selected from the group comprising beta-carotene, lutein, zeaxanthin, and lycopene, and 20 mg to 1000 mg of flavonoids comprising flavonoids obtainable from citrus fruits, red grapes, and elderberries; 20 mg to 200 mg of sulfur-containing amino acids selected from the group comprising L-cystine and/or

N-acetylcysteine; 20 mg to 200 mg of taurine; 50 mg to 1000 mg of omega-3 fatty acids, wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients, wherein a first solid dosage form comprises substances selected from the group comprising omega-3 fatty acids and carotenoids selected from the group comprising lutein, zeaxanthin, and lycopene, and wherein **a second liquid dosage form comprises** substances selected from the group comprising flavonoids obtainable from citrus fruits, **vitamins, and trace elements.**

EX1008 (Ortho Pharma) ¶[0008]. Ortho Pharma's preferred pharmaceutically acceptable carrier for this liquid formulation was water. For example, Ortho Pharma states:

The term "solution" as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein....A particularly preferred solvent is water.

EX1008 (Ortho Pharma), ¶[0038].

108. In another example, Ortho Pharma discloses that the solution contains: 200 mg of vitamin C, 600 µg of vitamin A, 73 mg of vitamin E, 2 mg of vitamin B₁, 2.5 mg of vitamin B₂, 20 mg of nicotinamide, 2.5 mg of vitamin B₆, 9 µg of vitamin B₁₂, 2.5 µg of vitamin D₃, 150 µg of biotin, 15 mg of zinc, 60 µg of selenium, 60 µg of chromium, 50 mg of taurine, 2 mg of beta-carotene, 36 mg of hesperidin available from citrus fruits;

EX1008 (Ortho Pharma) ¶[0056]. In contrast, a solid formulation delivers:

400 µg of folic acid, 15 mg of pantothenic acid, 16 mg of carotenoids, thereof 12 mg of lutein, 840 µg of zeaxanthin, 1 mg of lycopene, 10 mg of bioflavonoids available from red grapes, 4 mg of bioflavonoids available from elderberries, 258 mg of omega-3 fatty acids, thereof preferably 185 mg of docosahexaenoic acid, 50 mg of L-cystine.

EX1008 (Ortho Pharma) ¶[0056].

D. Widder (EX1009)

109. As I explained above, Widder published on January 19, 2006. For convenience, I will refer to this patent application publication as Widder.

110. Widder discloses compositions for use in treating ophthalmic conditions, such as macular degenerations and dystrophies, associated with the buildup of certain materials. At the same time, Widder identifies downsides to this approach. For example, Widder states:

Compounds that cause reversible **night blindness** may be used to treat ophthalmic conditions associated with the **overproduction of waste products that accumulate during the course of the visual cycle**. We describe methods and compositions using such compounds and their derivatives to treat, for example, the **macular degenerations and dystrophies** or to alleviate symptoms associated with such ophthalmic

conditions. Such compounds and their derivatives may be used as single agent therapy or in combination with other agents or therapies.

EX1009 (Widder), Abstract.

111. Widder thus teaches that (1) overproduction of waste products that accumulate during the course of the visual cycle contribute to macular degenerations and dystrophies; (2) compounds existed that could be used to treat these ocular disorders associated with overproduction of these waste products; and (3) these compounds caused night blindness. Widder discloses *in vitro* and animal data relating to treatments with such compounds, as well as describing an approach to be employed to assess treatment effectiveness in humans.

112. Widder elaborates on the role of the visual cycle in producing the toxic waste product A2E that contributes to lipofuscin and drusen formation. For example, Widder states:

Other proteins associated with the visual cycle are responsible for transporting, removing and/or disposing of compounds and **toxic products that accumulate from excess production of visual cycle retinoids**, such as all-trans-retinal (atRAL) [also known as ATR]. For example, N-retinylidene-N-retinylethanolamine (**A2E**) arises from the condensation of all-trans-retinal with phosphatidylethanolamine. Although certain levels of this orange-emitting fluorophore are tolerated by the photoreceptors and the

RPE, excessive quantities can lead to adverse effects, including the production of lipofuscin, and potentially drusen under the macula.

EX1009 (Widder), 1:17-22.

113. Widder also links the accumulation of these waste products to development of macular degeneration and retinal dystrophies. Widder states that:

[The] removal and disposal of toxic products that arise from side reactions in the visual cycle are important because several lines of evidence indicate that the over-accumulation of toxic products is partially responsible for the symptoms associated with the macular degenerations and retinal dystrophies.

EX1009 (Widder), 1:26-28.

114. Widder further explains that the disclosed compositions are useful for treating Stargardt Disease, which Widder describes as a “macular dystrophy that manifests as a recessive form of macular degeneration with an onset during childhood.” EX1009 (Widder), 17:5-6. Widder explains that “Stargardt Disease is associated with the deposition of lipofuscin pigment granules in RPE cells.”

EX1009 (Widder), 17:11-12. Widder further teaches that arresting accumulation of A2E and lipofuscin would be beneficial in an effort to treat Stargardt’s disease. For example, Widder discloses that administration of HPR “arrested accumulation of A2E and lipofuscin autofluorescence in the RPE” in “mice harboring mutation in the Stargardt’s disease gene (ABCA4)...reductions of visual chromophore were

manifest as modest delays in dark adaptation... chromophore regeneration kinetics were normal... These findings demonstrate the Vitamin A-dependent nature of A2E biosynthesis and validate a therapeutic approach which is readily transferable to human patients suffering from lipofuscin-based retinal diseases.” EX1009 (Widder), 51:9-16.

115. Recognizing the standard of care for macular degeneration existent by 2007, Widder states “[s]ome patients with dry form AMD have responded to high doses of vitamins and minerals.” EX1009 (Widder), 2:17-18.

116. Adding to this approach, Widder teaches that negatively charged phospholipids can be administered to remediate apoptosis of RPE cells induced by existent lipofuscin. Widder discloses that “[t]he use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies. *See, e.g.*, [EX1020, EX1021]. Examples of suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include cardiolipin and phosphatidylglycerol.” EX1009 (Widder), 33:1-7; *see also* EX1020 (Shaban & Richter), Abstract (stating that “[f]ree retinal...is phototoxic, and is a precursor of the (photo)toxic compound A2E, which...induces cell death by apoptosis. Cell death induced by A2E in the dark is prevented by negatively charged phospholipids.”); EX1021 (Shaban et al.), Abstract (stating that “A2E at low

concentrations causes apoptosis in cultured human retinal pigment epithelial cells....Phosphatidylglycerol, a negatively charged phospholipid and immediate biosynthetic precursor of cardiolipin readily inhibits apoptosis.”).

117. In addition to administering vitamins and minerals, and the aforementioned phospholipids, Widder employs compounds known to induce night blindness (i.e., compounds that interfere with the visual cycle) to slow lipofuscin formation. EX1009 (Widder), Abstract. Fenretinide (also called HPR) was prominent among Widder’s choice of such night-blindness inducing compounds. EX1009 (Widder), 14:22-31.

118. Widder explains that fenretinide targets the ocular tissue to prevent storage therein of vitamin A in the form of retinyl esters. For example, Widder states that:

Vitamin A in serum is delivered to extra-hepatic target tissues and immediately esterified by the membrane-bound enzyme LRAT [Lecithin retinol acyl transferase]. LRAT catalyzes the transfer of a fatty acid from membrane phospholipids to retinol thereby generating all-trans retinyl esters, the principal storage form of vitamin A in all tissues....N-4-(hydroxyphenyl)retinamide [fenretinide, or HPR] has been shown to cause marked inhibition of LRAT activity in membranes prepared from liver and small intestine. Additionally, we have demonstrated (e.g., Example 13) for

the first time that **LRAT activity in the RPE of the eye is inhibited by HPR**. As discussed in the Examples, administration of HPR is also associated with decreased serum retinol and retinol binding protein (RBP). Thus, in addition to the systemic effects of HPR (e.g., decreased serum retinol levels), there is also an intracellular, enzyme-specific effect (e.g., LRAT activity in RPE cells). The fact that vitamin A homeostasis in the eye relies not only upon delivery of retinol from serum but also upon intracellular stores of retinyl esters to provide visual chromophore, suggests that effects of HPR may be most pronounced in this organ.

EX1009 (Widder), 15:19-32. Widder thus teaches that fenretinide decreases serum retinol levels generally and reduces the storage of retinyl esters in RPE cells in the eye.

E. Mata (EX1010)

119. An article entitled “Biosynthesis of a major lipofuscin fluorophore in mice and humans with *ABCR*-mediated retinal and macular degeneration” was published in 2000 by Nathan L. Mata, Jian Weng, and Gabriel H. Travis in the periodical publication *Proceedings of the National Academy of Science* (PNAS). I will refer to this article as Mata.

120. Mata discloses that age-related macular degeneration was known to be common in the elderly and that is characterized by the accumulation of fluorescent

extracellular deposits and lipofuscin in retinal pigment epithelium (RPE) cells. For example, Mata states:

Age-related macular degeneration (AMD) is a common cause of blindness in the elderly. It is characterized by the accumulation of fluorescent extracellular deposits called drusen and fluorescent lipofuscin granules in cells of the retinal pigment epithelium (RPE).

EX1010 (Mata), 7154.

121. Mata further discloses that other forms of macular degeneration, including Stargardt's disease and the related condition fundus flavimaculatus, are also understood to be associated with lipofuscin accumulation in the RPE. For example, Mata states:

Lipofuscin accumulation in the RPE is also associated with Stargardt's disease (STGD1) and fundus flavimaculatus (FFM), recessive forms of macular degeneration that affect children.

EX1010 (Mata), 7154.

122. Additionally, Mata discloses the connection between Stargardt's disease, fundus flavimaculatus, and AMD, stating that:

These allelic disorders [Stargardt's disease and fundus flavimaculatus] are caused by mutations in ABCR....Heterozygous mutations in the ABCR gene may also predispose to AMD in a subset of cases....

EX1010 (Mata), 7154.

123. Mata studied intermediates of A2E, a major component of lipofuscin, which is associated with macular degeneration, in mice with both copies of the

ABCR gene inactivated, and identified two potential pathways for decreasing the progression of macular degeneration associated with lipofuscin formation. The first is to reduce the formation of all-*trans*-retinal, which Mata discusses may be done by “limiting exposure to light.” EX1010 (Mata), 7154. The second is to target the pathway involved in A2E formation. In relation to these approaches, Mata states that:

These data suggest that humans with retinal or macular degeneration caused by loss of [rim protein (an ATP-binding cassette transporter in rod outer segments)] function may slow progression of their disease by limiting exposure to light. The precursors of A2E identified in this study may represent pharmacological targets for the treatment of ABCR-mediated macular degeneration.

EX1010 (Mata), 7154.

124. Furthermore, Mata discloses that all-trans retinaldehyde (all-trans-RAL), a component of the light cycle, is involved in the process of forming A2E, and concludes that “[p]harmacological inhibition of one or more steps in the A2E synthetic pathway may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.” EX1010, 7159. Moreover, Mata (EX1010, Fig. 5) demonstrated the importance of the C-20 position in

dimerization and A2E formation, as discussed by Dr. Guengerich. EX1002, ¶¶219-21; *see also id.*, Sections VIII.B-C, IX.E (discussing Mata).

125. As such, a person of ordinary skill in the art in view of Mata would have good reason to formulate a pharmaceutical compound that inhibits A2E synthesis.

XI. [GROUND 1] CLAIMS 1-6, AND 28 ARE OBVIOUS OVER OLSON 1988 AND OLSON 1989

126. For each claim below, I will evaluate the four factors that I have been informed by Counsel are required to be applied in an obviousness analysis. I have discussed my evaluation of the first three factors (scope and content of prior art; differences between claim and prior art; and level of ordinary skill in the art) together below the claim language. For simplicity's sake and to avoid repetition, I have discussed my evaluation of the fourth factor (secondary indicia, and in particular the question of whether there were unexpected results) at the end of the claim listing. However, in providing my opinion regarding obviousness for each claim, I have considered all four factors.

A. Claim 1

a) Scope of Claim 1 of the '432 Patent and Content of the Prior

127. I have reproduced claim 1 of the challenged '432 patent below.

1. A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃ -retinoid and a pharmaceutically acceptable carrier, 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 a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

128. Both Olson 1988 and Olson 1989 published before 2007. They are found in the same field of the invention as the '432 patent (see Sections IV-VI above) and address the same problem addressed by the '432 patent.

129. Olson 1988 discloses C₂₀-D₃-retinol and a C₂₀-D₃-retinol acetate), both of which are members of the genus of C₂₀-deuterated retinoids recited in the claim. EX1006 (Olson 1988), Abstract, 12-13, 14, 15-19. Olson 1988 explains that these deuterated forms of vitamin A were made to study vitamin A metabolism in humans. EX1006 (Olson 1988), 11 (“For studying the metabolism of vitamin A in humans, nonradioactive deuterated or ¹³C labeled compounds of high purity are desired.”), Abstract (deuterated vitamin A created for “biological studies of vitamin A metabolism”).

130. A person of ordinary skill in the art would have understood that using deuterated vitamin A to study metabolism of vitamin A in humans would involve formulating the deuterated vitamin A in a pharmaceutically acceptable carrier for administration to humans, as was conventional. As such, Olson 1988 discloses claimed compounds and suggests the use of pharmaceutically acceptable carriers for their administration.

131. Olson 1989 corroborates that it was conventional to formulate deuterated vitamin A in a pharmaceutically acceptable carrier for biological studies. Olson 1989 teaches a pharmaceutical composition comprising a purified, deuterated vitamin A in a pharmaceutically acceptable carrier. EX1007 (Olson 1989), 713-14 & Abstract. To illustrate, Olson 1989 studied the effect of administering deuterated retinyl acetate to human subjects in order to estimate their vitamin A status. EX1007 (Olson 1989), 713 (stating that “[t]he vitamin A status of 11 generally healthy surgical patients was estimated by measuring the dilution of a 45-mg oral dose of *tetradeuterated retinyl acetate* (99% pure).” EX1007 (Olson 1989), 713. Olson 1989 discloses that the deuterated vitamin A was successfully formulated in corn oil. EX1007 (Olson 1989), 714 (stating that **each subject was given a 45 mg all-*trans* 10,19,19,19,19-²H₄retinol as retinyl acetate in corn oil.**”). This was the same pharmaceutically acceptable carrier used to formulate the non-deuterated vitamin A as well. Accordingly, Olson 1989 confirms that formulating deuterated vitamin A in a pharmaceutically acceptable carrier (e.g., corn oil) was conventional before 2007.

132. Furthermore, I have reviewed excerpts of the 19th edition of “Remington: The Science and Practice of Pharmacy” which was published in 1995 by *Mack Publishing Company* and authored by Alfonso R Gennaro. For the sake of

brevity, I will refer to this reference as Remington. Remington confirms that corn oil was a conventional pharmaceutically acceptable carrier.

133. Remington discloses that “[d]iluting agents (vehicles or *carriers*) are indifferent substances which are used as solvents for active materials.” EX1017 (Remington), 1392. Furthermore, Remington discloses corn oil as a carrier for injection as well as ingestion:

Uses—Main official use is a *solvent* and *vehicle for injections*. It is used as an edible oil substitute for solid fats in the management of hypercholesterolemia. Other uses include making soaps and for burning. It is a semidrying oil and therefore unsuitable for lubricating or mixing paint.

EX1017 (Remington), 1394. Remington thus corroborates the teaching of Olson 1989 that corn oil was a conventional pharmaceutically acceptable carrier.

134. In summary, Olson 1988 teaches the claimed C₂₀-deuterated vitamin A and suggests formulation in a pharmaceutically acceptable carrier by teaching it was created for biological studies. Olson 1989 corroborates that formulation of deuterated vitamin A in a pharmaceutically acceptable carrier was conventional. This disclosure supports concluding that the claims were obvious by 2007.

b) Differences Between What is Claimed and the Prior Art

135. There is no difference between what is claimed and what is taught and suggested in the prior art. As I explained above, Olson 1988 discloses the same

C₂₀-deuterated vitamin A that is claimed and discloses that it was created for use in biological studies in humans. A person of ordinary skill in the art would have understood that this use in biological studies involved formulation in a pharmaceutically acceptable carrier. Olson 1989 corroborates this, disclosing formulation of deuterated vitamin A in a pharmaceutically acceptable carrier for biological studies was conventional. The prior art disclosure of what is claimed supports concluding the claim was obvious by 2007.

c) Level of Skill in the Art

136. The level of skill in the art also supports concluding that what is claimed was obvious by 2007. As evidenced by Olson 1989 (as discussed above), it was well within the skill in the art to formulate deuterated vitamin A in a pharmaceutically acceptable carrier. Olson 1989 successfully used corn oil, which is identified in Remington as a conventional pharmaceutically acceptable carrier for injection or ingestion.

137. I note that the '432 patent does not assert that formulation in a pharmaceutically acceptable carrier is an inventive aspect of the patent or that any non-conventional formulation was required. Instead, the patent repeatedly admits that formulation was routine and conventional within the skill in the art and does not restrict the formulation to any particular approach. Indeed, the patent cites

Remington to support the ability to formulate the claimed compounds. For example, in relation to Remington, the '432 patent recites:

Pharmaceutically acceptable carriers are **well known in the art** (see, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen phosphate), sodium citrate, water, aqueous solutions (e.g., saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and tryglycerides [*sic*]), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, ***oils (e.g., corn***, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc. Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other

ingredients of the formulation and not injurious to the subject. *Carriers suitable for a selected dosage form and intended route of administration are well known in the art*, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

EX1001 (the '432 patent), 15:9-27. The challenged patent thus admits that formulation of the claimed compounds was conventional and within the level of ordinary skill in the art. It also thereby admits specifically that corn oil is a pharmaceutically acceptable carrier. Accordingly, the level of ordinary skill in the art supports a conclusion that the claim was obvious.

138. Well after the publication of Olson 1988 and 1989, the prior art provided an additional reason for a POSA to revisit formulation of Olson's C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier. As discussed in Section X.E, Mata discloses the biosynthetic pathway through which A2E, a major component of lipofuscin, forms in the eye, including the importance of C-20. As discussed in the declaration of Dr. Guengerich (EX1002), a chemist of ordinary skill would have recognized that C-20 deuteration would slow lipofuscin formation by 5-10 times because of the well-known deuterium kinetic isotope effect.

EX1002, Section VIII.C. Mata specifically suggests exploring inhibition of the A2E synthetic pathway as a strategy for treating macular degeneration. EX1010,

7159 (stating that “pharmacological inhibition of one or more steps in the A2E synthetic pathway may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation.”); *see* EX1002, Sections VIII.C, IX.E. In my opinion, and relying on Dr. Guengerich’s analysis of the kinetic isotope effect, a person of ordinary skill in the art would have had good reason to employ C₂₀-deuterated vitamin A, such as disclosed in Olson 1988, in place of vitamin A to slow and reduce the formation of lipofuscin in the eye. Accordingly, a person of ordinary skill in the art would have formulated C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier for administration in biological studies (e.g., in mice) to observe the reduced A2E and lipofuscin formation expected to result from this deuterium substitution.

139. A person of ordinary skill in the art would have good reason to slow the formation of lipofuscin using C₂₀-deuterated vitamin A, notwithstanding earlier experiments in reducing lipofuscin formation by restricting exposure to light (e.g., Mata) or restricting the supply of vitamin A to the ocular tissue (e.g., Widder). Each of these prior experiments presented room for improvement because of known downsides, including impairment of vision and discomfort (e.g., deprivation of light) or night blindness, related to restricting the supply of vitamin A to ocular tissue. Indeed, as I explained above, the compounds used to restrict the supply of vitamin A to ocular tissue presented known side effects. See Section

VIII.B. above. Accordingly, a person of ordinary skill in the art would have recognized that it would have been desirable to reduce lipofuscin associated with macular degeneration without incurring undesirable side effects of night blindness, as occurred with compounds such as fenretinide and isotretinoin.

140. Indeed, in macular degenerations involving lipofuscin formation, in lieu of restricting Vitamin A pharmacologically, a person of ordinary skill in the art would have recognized that C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier would have been desirable to partially replace the non-deuterated vitamin A in the ocular tissue, thus maintaining the visual cycle and retinal function while reducing A2E and lipofuscin formation. Additionally, a person of ordinary skill in the art would have understood that C₂₀-deuterated vitamin A could potentiate the effect of drugs such as fenretinide and isotretinoin, permitting these drugs to be used at lower dosages where side effects such as night blindness could be less prominent. Furthermore, and as discussed above in Sections VIII.D-E., deuterated forms of vitamin A had been administered to humans in pharmaceutically acceptable carriers for decades without incident and there was significant interest in deuterated forms of existing therapeutics.

141. For the reasons discussed above, the desire to reduce lipofuscin formation by inhibiting the A2E synthesis pathway without depriving the body and ocular tissues of vitamin A and without interfering with the visual cycle provided

additional reason to formulate C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier.

142. In view of the three factors discussed above as well as the fourth factor discussed below in Section XIV, claim 1 as a whole was obvious before 2007.

B. Claims 2-3: Tri-Deutero Vitamin A

2. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal and a C₂₀-D₃-pro-vitamin A carotenoid.

3. The pharmaceutical composition according to claim 2, wherein the substituted C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.

143. Claims 2 and 3 specify the substituted C₂₀-D₁₋₃-retinoid of claim 1.

Claims 2 and 3 are still satisfied by the specific C₂₀-deuterated vitamin A (C₂₀-D₃-retinol acetate) disclosed in Olson 1988. As discussed above and in the declaration of Dr. Guengerich, Olson 1988 discloses C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). *See* Section XI.A; EX1002, ¶¶190, 200-12.

Accordingly, claims 2 and 3 are obvious for the same reasons I explained for claim 1 above.

C. Claim 4: Dosage Forms

4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form.

144. Claim 4 depends from claim 1 and further recites the pharmaceutical composition is in unit dosage form. As discussed above, claim 1 is obvious over Olson 1988 and Olson 1989. Olson 1989 discloses the use of a unit dosage form (e.g., 45 mg oral dose) of a deuterated vitamin A analog. EX1007 (Olson 1989), 713 (stating that “The vitamin A status in 11 generally healthy surgical patients was estimated by measuring the dilution of a 45-mg oral dose of tetradeuterated retinyl acetate (99% pure).”). Additionally, unit dose forms such as eyedrops, implants, and injections were commonly used for retinal conditions. Accordingly, it is my opinion that claim 4 as a whole is obvious over Olson 1988 and Olson 1989.

D. Claims 5-6 and 28: Reduced A2E Formation

5. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

6. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

28. The pharmaceutical composition according to claim 3, wherein the C₂₀-D₁₋₃-retinoid corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

145. As discussed above, claim 1 is obvious over Olson 1988 and Olson 1989. Claims 5, 6, and 28 are directed to slowing the formation of A2E and/or all-trans-retinal (ATR)-dimer compared to a corresponding non-deuterated enriched

retinoid. I understand from Dr. Guengerich (EX1002) that the additional elements of these claims encompass the natural property of C₂₀-D₃-all-trans-retinal that due to the kinetic isotope effect it inhibits the formation of A2E (claim 6) or forms A2E 7 times slower (claims 5 and 28) as compared to the non-deuterium-enriched all-trans-retinal. *See* EX1002, ¶¶217-22. Accordingly, each of claims 5, 6, and 28 is obvious over Olson 1988 and Olson 1989.

XII. [GROUND 2] CLAIMS 1-6, 8-23, 25 AND 27-28 ARE OBVIOUS OVER OLSON 1988 AND ORTHO PHARMA 2006

146. For at least the reasons discussed below, it is my opinion that claims 1-6, 8-23, 25 and 27-28 of the challenged '432 patent are obvious as a whole. The obviousness of these claims is demonstrated by the Olson 1988 and Ortho Pharma references.

147. As discussed above under Ground 1 in Section XI, Olson 1988 discloses synthesizing and purifying the claimed C₂₀-D₁₋₃-retinoids. My below analysis for Ground 2 applies the teachings of Ortho Pharma.

148. Ortho Pharma, which is discussed under Section X.C. above, discloses compositions comprising vitamin A in a pharmaceutically acceptable carrier (e.g., water), along with additives (e.g., vitamin C, vitamin E, vitamin D, and zinc), antioxidants (e.g., vitamin C, vitamin E, and beta-carotene), and minerals (e.g.,

zinc and selenium) in a unit dosage form. For example, Ortho Pharma discloses that:

[B]ased on a *daily dose* of the carotenoid-containing product, as active ingredients the substances: 50 mg to 500 mg of *vitamin C*, 0.1 mg to 2 mg of *vitamin A*, 10 mg to 400 mg of *vitamin E*...0.1 µg to 10 µg of *vitamin D₃*... 2 mg to 30 mg of *zinc*....20 µg to 100 µg of *selenium*...wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients...wherein a *second liquid dosage form* comprises substances selected from the group comprising flavonoids obtainable from citrus fruits, vitamins, and trace elements.

EX1008 (Ortho Pharma), ¶[0008].

149. Ortho Pharma further discloses a preference for water as the solvent for the vitamins and minerals in the liquid solution. In particular, Ortho Pharma states that “[t]he term “solution” as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein....A *particular preferred solvent is water*. EX1008 (Ortho Pharma), ¶[0038].

150. Ortho Pharma discloses that the liquid form of the carotenoid-containing product is both well tolerated and helps with different aspects relating to the absorption of the ingredients. For example, Ortho Pharma states that “[i]t has been shown, for example, that administration in a liquid dosage form is a particularly well-tolerated form of administration for some ingredients, in particular flavonoids from citrus fruits, vitamins, and trace elements. EX1008 (Ortho Pharma), ¶[0012]. Ortho Pharma further states that “the liquid dosage form can also provide increased solubility of the components....Advantageously, the

flavonoids obtainable from citrus fruits, **vitamins, and trace elements** contained **in the liquid dosage form** can be absorbed by the body much better compared to a usual dosage form as tablet or capsule. EX1008 (Ortho Pharma), ¶¶[0014]-[0015]. Accordingly, it also would have been obvious for the liquid dosage form to use a hydrophobic pharmaceutically acceptable carrier (e.g., corn oil as used in Olson 1989) for fat soluble components including vitamins A and E and flavonoids.

151. Additionally, Ortho Pharma discloses the use of a pharmaceutically acceptable excipients in the composition, such as humectants (e.g., glycerol and starch), vegetable oil, stabilizers (e.g., gum Arabic), and carriers (e.g., silicon dioxide). For example, Ortho Pharma discloses:

In preferred embodiments, the carotenoid-containing product may comprise at least one additive, *preferably several additives*....Usual additives and/or auxiliaries known to the person skilled in the art are suitable. Particularly preferred are additives selected from the group comprising humectants such as *glycerol, starch*, preferably modified starch, in particular from wheat and/or corn, *vegetable oil*, gelatin, maltodextrin, stabilizers such as *gum arabic*, preservatives such as potassium sorbate, sweeteners such as acesulfame K, sodium cyclamate, and/or saccharin sodium, *carriers such as silicon dioxide*, flavors, and/or colorants such as iron oxide.

EX1008 (Ortho Pharma), ¶[0050]-[0051].

152. Ortho Pharma further discloses that the carotenoid-containing composition comprises an additional active agent, such as a carotenoid (e.g., beta-carotene, zeaxanthin, and lutein). For example, Ortho Pharma states:

based on a daily dose of the carotenoid-containing product, *carotenoids* selected from the group consisting of: 5 mg to 20 mg, preferably 6 mg to 15

mg, preferred 10 mg to 12 mg of ***lutein***, and/or 200 µg to 1200 µg, preferably 300 µg to 1000 µg, preferred 500 µg to 850 µg of ***zeaxanthin***...and/or 0.5 mg to 5 mg, preferably 1 mg to 3 mg, preferred 1.5 mg to 2.5 mg of ***beta-carotene***.

EX1008 (Ortho Pharma), ¶[0024]. Ortho Pharma states that the carotenoid-containing product is useful for treating or preventing eye diseases, such as macular degeneration. For example, Ortho Pharma states:

Advantageously, a supplementary diet and/or a supportive dietary treatment with the carotenoid-containing product according to the invention can, for example, show positive effects on the health of the eye in the case of an ***existing macular degeneration*** or senile cataract, as well as ***counteract a macular degeneration*** or senile cataract.

EX1008 (Ortho Pharma), ¶[0011].

153. Similarly, Ortho Pharma also discloses that the carotenoid-containing product can be used as a food to provide nutrients and that diet can influence age-related diseases, such as macular degeneration. To illustrate, Ortho Pharma states:

Due to the advantageous active ingredients of the carotenoid-containing product, it ***can also be used as a food, in particular a food supplement***, in the context of nutritional counseling. Preferably, the food, in particular food supplement, comprises the aforementioned active ingredients. Preferably, the carotenoid-containing product can be used as a nutritive supplement for adjunctive or supportive administration. It has been shown that ***in particular age-related eye diseases such as age-related macular degeneration or senile cataract can be positively influenced by diet***.

EX1008 (Ortho Pharma), ¶[0054]. Ortho Pharma further states:

The carotenoid-containing product can be used for ***dietary treatment of age-related eye diseases***. Furthermore, the carotenoid-containing product can be used for the preparation of an agent for the dietary treatment of age-related eye diseases such as age-related macular degeneration or senile cataract. The carotenoid-containing product according to the invention is also ***suitable as a***

balanced dietary supplement for patients with age-related eye diseases such as age-related macular degeneration or senile cataract. The carotenoid-containing product according to the invention is particularly suitable as a supplementary balanced diet.

EX1008 (Ortho Pharma), ¶[0052].

A. Claim 1

a) Scope of Claim 1 of the '432 Patent and Content of the Prior

154. I have reproduced claim 1 of the challenged '432 patent below.

1. A pharmaceutical composition comprising a substituted C₂₀-D₁₋₃ -retinoid and a pharmaceutically acceptable carrier, 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 a C₂₀-D₁₋₃-pro-vitamin A carotenoid.

155. Both Olson 1988 and Ortho Pharma published before 2007. They are found in the same field of the invention as the '432 patent (see Sections IV-VI above) and address the same problem addressed by the '432 patent.

156. As discussed above for Ground 1 in Section XI.A above, Olson 1988 discloses C₂₀-D₁₋₃-retinoids, such as C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate) as recited in claim 1 of the challenged '432 patent. EX1006 (Olson 1988), Abstract, 12-13, 14, 15-19. Furthermore, Olson 1988 makes the claimed compounds for the purpose of using them in biological studies.

157. As evidenced by my discussion of Ortho Pharma 2006 in Section X.C. of this declaration, Ortho Pharma teaches making and using compositions

comprising vitamin A in a pharmaceutically acceptable carrier (e.g., water, oil, etc.). For example, Ortho Pharma states:

[B]ased on a **daily dose** of the carotenoid-containing product, as active ingredients the substances: 50 mg to 500 mg of vitamin C, 0.1 mg to 2 mg of **vitamin A**, 10 mg to 400 mg of vitamin E...0.1 µg to 10 µg of vitamin D₃...2 mg to 30 mg of zinc...20 µg to 100 µg of selenium...wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients...wherein a **second liquid dosage form** comprises substances selected from the group comprising flavonoids obtainable from citrus fruits, vitamins, and trace elements.

EX1008 (Ortho Pharma), ¶[0008].

158. Ortho Pharma discloses a preference for water as the solvent for the vitamins and minerals and in the liquid dosage form. In particular, Ortho Pharma states that “[t]he term ‘solution’ as used in the present invention means a mixture of a solvent and substances dissolved, suspended and/or emulsified therein....A **particular preferred solvent is water.**” EX1008 (Ortho Pharma), ¶[0038].

159. Ortho Pharma also provides that the composition can contain an additive, and in some cases, even more than one additive (e.g., glycerol, starch, vegetable oil, gum Arabic, and silicon dioxide). For example, Ortho Pharma states:

In preferred embodiments, the carotenoid-containing product may comprise **at least one additive, preferably several additives**....Usual additives and/or auxiliaries known to the person skilled in the art are suitable. Particularly preferred are additives selected from the group comprising humectants such as **glycerol, starch**, preferably modified starch, in particular from wheat and/or corn, **vegetable oil**, gelatin, maltodextrin, stabilizers such as **gum arabic**, preservatives such as potassium sorbate, sweeteners such as

acesulfame K, sodium cyclamate, and/or saccharin sodium, *carriers such as silicon dioxide*, flavors, and/or colorants such as iron oxide.

EX1008 (Ortho Pharma), ¶¶[0050]-[0051].

160. Ortho Pharma thus corroborates that it was conventional to formulate deuterated vitamin A in a pharmaceutically acceptable carrier for administration to animals.

161. Furthermore, Remington confirms that water was a conventional pharmaceutically acceptable carrier. The '432 patent acknowledges that water is a pharmaceutically acceptable carrier that was known in the art. EX1001, 15:9-26 (citing “Remington’s Pharmaceutical Sciences” and admitting that formulation of the claimed compounds is done “by conventional methods known to those of skill in the art” and that carriers suitable for a selected dosage form “can be determined using ordinary skill in the art”). Additionally, in a short list of pharmaceutically acceptable “diluting agents (vehicles or carriers),” Remington teaches that water is an appropriate vehicle and solvent for oral administration or external application. EX1017, 21-23.

162. Remington thus corroborates the teaching of Ortho Pharma that water was a conventional pharmaceutically acceptable carrier. Moreover, as discussed above regarding Olson 1989, other pharmaceutically acceptable carriers (e.g., corn oil) were known to be useful for formulating deuterated vitamin A for

administration to humans, and Remington corroborates that these hydrophobic pharmaceutically acceptable carriers also were routinely employed.

163. In summary, Olson 1988 teaches the claimed C₂₀-deuterated vitamin A and suggests formulation in a pharmaceutically acceptable carrier by teaching it was created for biological studies. Ortho Pharma corroborates that formulation of vitamin A in a pharmaceutically acceptable carrier was conventional. This disclosure supports concluding that the claims were obvious by 2007.

b) Differences Between What is Claimed and the Prior Art

164. There is no difference between what is claimed and what is taught and suggested in the prior art. As I explained above, Olson 1988 discloses the same C₂₀-deuterated vitamin A that is claimed and discloses that it was created for use in biological studies in humans. A person of ordinary skill in the art, such as an ophthalmologist working as a member of a development team including a chemist or pharmacologist, would have understood that this use in biological studies involved formulation in a pharmaceutically acceptable carrier. Ortho Pharma corroborates that it was conventional to formulate vitamin A in a pharmaceutically acceptable carrier for administration to animals. The prior art disclosure of what is claimed supports concluding the claim was obvious by 2007.

c) Level of Skill in the Art

165. The level of skill in the art also supports concluding that what is claimed was obvious by 2007. As evidenced by Ortho Pharma (as discussed above), it was well within the skill in the art to formulate vitamin A in a pharmaceutically acceptable carrier. Ortho Pharma taught that water was a preferred solvent, which is identified in Remington as a conventional pharmaceutically acceptable carrier.

166. I note that the '432 patent does not assert that formulation in a pharmaceutically acceptable carrier is an inventive aspect of the patent or that any non-conventional formulation was required. Instead, the patent repeatedly admits that formulation was routine and conventional within the skill in the art and does not restrict the formulation to any particular approach. Indeed, the patent cites Remington to support the ability to formulate the claimed compounds. For example, in relation to Remington, the '432 patent recites:

Pharmaceutically acceptable carriers are **well known in the art** (see, e.g., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, Pa.) and The National Formulary (American Pharmaceutical Association, Washington, D.C.)) and include sugars (e.g., lactose, sucrose, mannitol, and sorbitol), starches, cellulose preparations, calcium phosphates (e.g., dicalcium phosphate, tricalcium phosphate and calcium hydrogen

phosphate), sodium citrate, **water, aqueous solutions** (e.g., saline, sodium chloride injection, Ringer's injection, dextrose injection, dextrose and sodium chloride injection, lactated Ringer's injection), alcohols (e.g., ethyl alcohol, propyl alcohol, and benzyl alcohol), polyols (e.g., glycerol, propylene glycol, and polyethylene glycol), organic esters (e.g., ethyl oleate and triglycerides [*sic*]), biodegradable polymers (e.g., polylactide-polyglycolide, poly(orthoesters), and poly(anhydrides)), elastomeric matrices, liposomes, microspheres, oils (e.g., corn, germ, olive, castor, sesame, cottonseed, and groundnut), cocoa butter, waxes (e.g., suppository waxes), paraffins, silicones, talc, silicylate, etc. Each pharmaceutically acceptable carrier used in a pharmaceutical composition of the invention must be "acceptable" in the sense of being compatible with the other ingredients of the formulation and not injurious to the subject. ***Carriers suitable for a selected dosage form and intended route of administration are well known in the art***, and acceptable carriers for a chosen dosage form and method of administration can be determined using ordinary skill in the art.

EX1001 (the '432 patent), 15:9-27.

167. The challenged patent thus admits that formulation of the claimed compounds was conventional and within the level of ordinary skill in the art. It also thereby admits specifically that water is a pharmaceutically acceptable carrier. Accordingly, the level of ordinary skill in the art supports a conclusion that the claim was obvious.

168. Well after the publication of Olson 1988, the prior art provided an additional reason for a POSA to revisit formulation of Olson's C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier. As discussed in Section X.E, Mata discloses the biosynthetic pathway through which A2E, a major component of lipofuscin, forms in the eye. As discussed in the declaration of Dr. Guengerich (EX1002), a chemist of ordinary skill would have recognized that C-20 deuteration would slow lipofuscin formation by 5-10 times because of the well-known deuterium kinetic isotope effect. EX1002, ¶¶231-34, 311-13; *see also id.*, Sections VIII.B, IX.E (discussing Mata). Mata specifically suggests exploring inhibition of the A2E synthetic pathway as a strategy for treating macular degeneration, and Mata's research (Fig. 5) indicated that the C-20 position would be a useful site for inhibition of A2E formation. EX1010, 7159 (stating that "pharmacological inhibition of one or more steps in the A2E synthetic pathway may thus be an effective treatment strategy for other macular degenerations associated with lipofuscin accumulation."). In my opinion, a person of ordinary skill in the art

would have had good reason to employ C₂₀-deuterated vitamin A, such as disclosed in Olson 1988, in place of Ortho Pharma's vitamin A to slow and reduce the formation of lipofuscin in the eye. Accordingly, a person of ordinary skill in the art would have formulated C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier for administration to animals (e.g., in mice) to observe the reduced lipofuscin formation expected to result from this deuterium substitution.

169. A person of ordinary skill in the art would have good reason to slow the formation of lipofuscin using C₂₀-deuterated vitamin A notwithstanding earlier experiments in reducing lipofuscin formation by restricting exposure to light (e.g., Mata) or restricting the supply of vitamin A to the ocular tissue (e.g., Widder). Each of these prior experiments presented room for improvement because of known downsides, including impairment of vision and discomfort (e.g., deprivation of light) or night blindness due to restricting the supply of vitamin A to ocular tissue. Indeed, as I explained above, the compounds used to restrict the supply of vitamin A to ocular tissue presented known side effects. See Section VIII.B above. Accordingly, a person of ordinary skill in the art would have recognized that it would have been desirable to reduce lipofuscin associated with macular degeneration without unnecessarily incurring undesirable side effects night-blindness, as had been observed with drugs such as fenretinide and isotretinoin. Indeed, a person of ordinary skill in the art would have recognized that

C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier would have been desirable to partially replace the non-deuterated vitamin A in the ocular tissue, thus maintaining the visual cycle and retinal function while reducing A2E and lipofuscin formation. Additionally, a person of ordinary skill in the art would have understood that C₂₀-deuterated vitamin A could potentiate the effect of drugs such as fenretinide and isotretinoin, permitting these drugs to be used at lower dosages where side effects such as night blindness could be less prominent. Furthermore, and as discussed above in Sections VIII.D-E., deuterated forms of vitamin A had been administered to humans in pharmaceutically acceptable carriers for decades without incident and there was significant interest in deuterated forms of existing therapeutics.

170. For the reasons discussed above, the desire to reduce lipofuscin formation by inhibiting the A2E synthesis pathway without depriving the body and ocular tissues of vitamin A and without interfering with the visual cycle and visual function provided additional reason to formulate C₂₀-deuterated vitamin A in a pharmaceutically acceptable carrier, as described by Dr. Guengerich in his Declaration. *See* EX1002, Sections XII.A, XII.M-N.

171. In view of the three factors discussed above as well as the fourth factor discussed below in Section XIV, claim 1 as a whole was obvious before 2007.

B. Claims 2-3: Tri-Deutero Vitamin A

2. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid is selected from the group consisting of C₂₀-D₃-retinol, C₂₀-D₃-retinol ester, C₂₀-D₃-retinal and a C₂₀-D₃-pro-vitamin A carotenoid.

3. The pharmaceutical composition according to claim 2, wherein the substituted C₂₀-D₁₋₃-retinoid is C₂₀-D₃-retinol acetate.

172. Claims 2 and 3 specify the substituted C₂₀-D₁₋₃-retinoid of claim 1.

Claims 2 and 3 are still satisfied by the specific C₂₀-deuterated vitamin A (C₂₀-D₃-retinol acetate) disclosed in Olson 1988. As discussed above and in the declaration of Dr. Guengerich, Olson 1988 discloses C₂₀-D₃-retinol and a C₂₀-D₃-retinol ester (e.g., C₂₀-D₃-retinol acetate). *See* Sections XI.A. and XII.A; EX1002, ¶¶190, 200-12, 263-71. Accordingly, claims 2 and 3 are obvious for the same reasons I explained for claim 1 above.

C. Claim 4: Dosage Forms

4. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is in unit dosage form.

173. Claim 4 depends from claim 1 and further recites the pharmaceutical composition is in unit dosage form. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. As demonstrated above, Ortho

Pharma discloses a unit dosage form of a composition comprising vitamin A and a pharmaceutically acceptable carrier. For example, Ortho Pharma discloses:

based on a *daily dose* of the carotenoid-containing product, as active ingredients the substances...0.1 mg to 2 mg of *vitamin A*...wherein the product is in the form of at least two separately present dosage forms of different composition of active ingredients...a second *liquid dosage form* comprises substances selected from the group comprising flavonoids obtainable from citrus fruits, vitamins, and trace elements.

EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma also discloses that the “solution was in a drinking vial.” EX1008 (Ortho Pharma), ¶[0058].

174. Accordingly, it is my opinion that claim 4 as a whole is obvious over Olson 1988 and Ortho Pharma.

D. Claims 5-6 and 28: Reduced A2E Formation

5. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid, corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

6. The pharmaceutical composition according to claim 1, wherein the substituted C₂₀-D₁₋₃-retinoid inhibits the formation of A2E and/or ATR-dimer compared with the corresponding non-deuterium enriched retinoid.

28. The pharmaceutical composition according to claim 3, wherein the C₂₀-D₁₋₃-retinoid corresponding to the aldehyde of the C₂₀-D₁₋₃-retinol acetate, forms A2E in vitro about 7 times slower than non-deuterium-enriched retinoid.

175. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma.

176. Claims 5, 6, and 28 are directed to slowing the formation of A2E and/or all-trans-retinal (ATR)-dimer compared to a corresponding non-deuterium enriched retinoid.

177. As discussed above under Ground 1, Section XI.D., and as set forth in the declaration of Dr. Guengerich, the additional elements of these claims encompass the natural property of C₂₀-D₃-all-trans-retinal that it inhibits the formation of A2E (claim 6) or forms A2E 7 times slower (claims 5 and 28) as compared to the non-deuterium-enriched all-trans-retinal, due to the well-known kinetic isotope effect. *See* EX1002, ¶¶217-22, 276-78. As such, the claimed slowing is an inherent property of C₂₀-D₃-retinal. As I described under claim 1, C₂₀-D₃-retinal in a pharmaceutical carrier is obviated by Olson 1988 and Ortho Pharma. Accordingly, each of claims 5, 6, and 28 is obvious over Olson 1988 and Ortho Pharma.

E. Claims 8-9: Additives

8. The pharmaceutical composition according to claim 1, further comprising one or more additives.

9. The pharmaceutical composition according to claim 8, wherein the additives are selected from the group consisting of zinc, vitamin E, vitamin D, and combinations thereof.

178. Claims 8 and 9 are both directed to a pharmaceutical composition of claim 1 that further comprise an additive selected from zinc, vitamin E, vitamin D, and combinations thereof. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses a composition comprising zinc, vitamin E, and vitamin D, satisfying each of claims 8-9.

179. For example, Ortho Pharma states:

based on a daily dose of the carotenoid-containing product, as active ingredients the substances...0.1 mg to 2 mg of vitamin A; 10 mg to 400 mg of *vitamin E*...0.1 µg to 10 µg of *vitamin D₃*...2 mg to 30 mg of *zinc*....

EX1008 (Ortho Pharma), ¶[0008].

180. Accordingly, it is my opinion that each of claims 8 and 9 is obvious over Olson 1988 and Ortho Pharma.

F. Claims 10-12: Zinc Additives

10. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 80 mg.

11. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 3 to about 10 mg.

12. The pharmaceutical composition according to claim 9, wherein the zinc is present in the pharmaceutical composition at between about 10 to about 80 mg.

181. Claims 10-12 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 3 mg to about 10 mg of zinc. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses zinc amount in a range overlapping with the ranges recited in each of claims 10-12.

182. For example, Ortho Pharma discloses compositions comprising “based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*2 mg to 30 mg of zinc.*” EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma also discloses that “the carotenoid-containing product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*5 mg to 25 mg, preferably 10 mg to 20 mg of zinc.*” EX1008 (Ortho Pharma), ¶[0019]. The 2 mg to 30 mg, 5 mg to 25 mg, and 10 mg to 20 mg ranges of zinc provide by Ortho Pharma all overlap with the ranges of zinc recited in claims 10-12 of the challenged '432 patent. Accordingly, it is my opinion that each of claims 10-12 is obvious over Olson 1988 and Ortho Pharma.

G. Claims 13-15: Vitamin E Additives

13. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 3,000 mg.

14. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 3 to about 15 mg.

15. The pharmaceutical composition according to claim 9, wherein the vitamin E is present in the pharmaceutical composition at between about 15 to about 3,000 mg.

183. Claims 13-15 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 3 mg to about 15 mg of vitamin E. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses vitamin E amount in a range overlapping with the ranges recited in each of claims 13-15.

184. For example, Ortho Pharma discloses that “the carotenoid-containing product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...***10 mg to 400 mg of vitamin E.***” EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma also discloses that “the carotenoid-containing product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances....***20 mg to 200 mg, preferably 56 mg to 77 mg of vitamin E***” EX1008 (Ortho Pharma), ¶[0019]. The 10 mg to 400 mg, 20 mg to 200 mg, and 56 mg to 77 mg ranges of vitamin E disclosed in Ortho Pharma overlap with the ranges of vitamin E recited in claims 13-15 of the challenged '432 patent. Accordingly, it is my opinion that each of claims 13-15 is obvious over Olson 1988 and Ortho Pharma.

H. Claims 16-18: Vitamin D Additives

16. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.1 mg.

17. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.005 to about 0.015 mg

18. The pharmaceutical composition according to claim 9, wherein the vitamin D is present in the pharmaceutical composition at between about 0.015 to about 0.1 mg

185. Claims 16-18 are all directed to a pharmaceutical composition of claim 1 that further comprises between about 0.005 mg to about 0.015 mg of vitamin D. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses vitamin D amount in a range overlapping with the ranges recited in each of claims 16-18.

186. For example, Ortho Pharma discloses that “the carotenoid-containing product comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*0.1 µg to 10 µg of vitamin D₃*.” EX1008 (Ortho Pharma), ¶[0008]. Ortho Pharma further discloses that “based on 100 g of the carotenoid-containing product, wherein the weight contents of the individual components are selected such that the total weight of the components does not exceed 100 g, as active ingredients the substances...*0.4 µg to 45 µg, preferably 4.4 µg to 23 µg, preferred 8.5 µg to 14 µg of vitamin D₃*.” EX1008 (Ortho Pharma), ¶[0036].

187. The 0.1 µg to 10 µg (0.0001 mg to 0.01 mg) range of vitamin D₃ disclosed in Ortho Pharma overlaps with the ranges of vitamin D₃ recited in claims 16 and 17. The 0.4 µg to 45 µg, (0.0004 mg to 0.045 mg), 4.4 µg to 23 µg (0.0044 mg to 0.023 mg), and 8.5 µg to 14 µg (0.0085 mg to 0.014 mg) ranges of vitamin D₃ disclosed in Ortho Pharma overlap with the ranges of vitamin D₃ recited in claim 18. Accordingly, it is my opinion that each of claims 16-18 is obvious over Olson 1988 and Ortho Pharma.

I. Claim 19: Retinoid Concentrations

19. The pharmaceutical composition according to claim 1, wherein the C₂₀-D₁₋₃-retinoid is present in the pharmaceutical composition at a level sufficient to deliver on average about 0.1 to about 90 mg/day to a patient.

188. Claim 19 is directed to a pharmaceutical composition of claim 1 wherein the C₂₀-D₁₋₃ retinoid is present in the pharmaceutical composition at a level sufficient to deliver about 0.1 mg/day to about 90 mg/day on average to a patient. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses vitamin A amount in a range overlapping with the range recited in claim 19.

189. For example, Ortho Pharma discloses “a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...*0.1 mg to 2 mg of*

vitamin A....” EX1008 (Ortho Pharma), ¶[0008]. The 0.1 mg to 2 mg range of vitamin A disclosed by Ortho Pharma overlaps with the range recited in claim 19 of the challenged ’432 patent. Accordingly, it is my opinion that claim 19 is obvious over Olson 1988 and Ortho Pharma.

J. Claims 20-23: Additional Actives

20. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition comprises an additional active.

21. The pharmaceutical composition according to claim 20, wherein the additional active is selected from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof.

22. The pharmaceutical composition according to claim 21, wherein the eye antioxidant is selected from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a Trolox analog (PNU-83836-E), bilberry extract, and combinations thereof.

23. The pharmaceutical composition according to claim 21, wherein the mineral is selected from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

190. Claims 20-23 are all directed to a pharmaceutical composition of claim 1 that further comprises an additional active. Claim 21 depends from claim 20 and is directed to an additional active from the group consisting of eye antioxidants, minerals, negatively-charged phospholipids, carotenoids, and combinations thereof. Claim 22 depends from claim 21 and is directed to an eye

antioxidant from the group consisting of vitamin C, vitamin E, beta-carotene, coenzyme Q, OT-551, 4-hydroxy-2,2,6,6-tetramethylpiperidine-N-oxyl, butylated hydroxytoluene, resveratrol, a Trolox analog (PNU-83836-E), bilberry extract, and combinations thereof. Claim 23 depends from claim 21 and is directed to a mineral from the group consisting of cupric oxide, zinc oxide; selenium-containing compounds, and combinations thereof.

191. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses an additional active agent of eye antioxidants (e.g., vitamin C, vitamin E, and beta-carotene), minerals (e.g., selenium and sodium selenate), and carotenoids (e.g., zeaxanthin and lutein). For example, Ortho Pharma states:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...50 mg to 500 mg of *vitamin C*...0.1 mg to 2 mg of *vitamin A*...10 mg to 400 mg of *vitamin E*...20 µg to 100 µg of *selenium*...secondary plant compounds selected from the group comprising 6 mg to 32 mg of carotenoids comprising carotenoids selected from the group comprising *beta-carotene, lutein, zeaxanthin*....

EX1008 (Ortho Pharma), ¶[0008]. Furthermore, Ortho Pharma states:

In preferred embodiments, the carotenoid-containing product may contain active ingredients in the form of substances selected from the group consisting of orange juice concentrate, fish oil, sodium L-ascorbate, *vitamin E*, ascorbic acid, citrus extract, taurine, L-cystine, *zinc (II) chloride*, nicotinamide, calcium D-pantothenate, red grape extract, *carotenoids* comprising *lutein*, lycopene, and *zeaxanthin*, elderberry extract, vitamin B₆ hydrochloride, vitamin B₁ hydrochloride, vitamin B₂, *beta-carotene*, vitamin A acetate, folic

acid, chromium (III) chloride, biotin, *sodium selenate*, vitamin B₁₂, and/or vitamin D3.

EX1008 (Ortho Pharma), ¶[0049].

192. As such, Ortho Pharma discloses an additional active agent within the scope of each of claims 20-23. Accordingly, it is my opinion that each of claims 20-23 is obvious over Olson 1988 and Ortho Pharma.

K. Claim 25: Carotenoid

25. The pharmaceutical composition according to claim 1, wherein the carotenoid is selected from the group consisting of zeaxanthin, lutein, and combinations thereof.

193. Claim 25 is directed to a pharmaceutical composition of claim 1 that further comprises a carotenoid from the group consisting of zeaxanthin, lutein, and combinations thereof. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Ortho Pharma also discloses an additional active agent of carotenoids (e.g., zeaxanthin and lutein).

194. For example, Ortho Pharma states:

a carotenoid-containing product, in particular suitable for nutritive balanced supplementation of the diet in age-related eye diseases, which comprises, based on a daily dose of the carotenoid-containing product, as active ingredients the substances...50 mg to 500 mg of vitamin C...0.1 mg to 2 mg of vitamin A...10 mg to 400 mg of vitamin E...20 µg to 100 µg of selenium...secondary plant compounds selected from the group comprising **6 mg to 32 mg of carotenoids** comprising carotenoids selected from the group comprising beta-carotene, *lutein, zeaxanthin*....

EX1008 (Ortho Pharma), ¶[0008].

195. Accordingly, it is my opinion that claim 25 is obvious over Olson 1988 and Ortho Pharma.

L. Claim 27: Nutraceuticals

27. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is suitable for use as a nutraceutical composition.

196. Claim 27 is directed to a pharmaceutical composition of claim 1 that is suitable for use as a nutraceutical composition. As evidenced by Bull et al., the term “nutraceutical” refers to “medicinally or nutritionally functional foods.” EX1049 (Bull), 1. In other words, a nutraceutical is a nutrient substance or dietary supplement that is not necessarily FDA-approved to prevent or treat illness or disease but is suggested to have therapeutic or health benefits. As I have previously addressed above, claim 1 is obvious over Olson 1988 and Ortho Pharma. Furthermore, Ortho Pharma discloses a nutraceutical composition.

197. Ortho Pharma discloses that the product can be ingested for nutritional and health benefits, namely for treating or preventing age-related diseases, such as macular degeneration. For example, Ortho Pharma states:

The present invention relates to 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.

EX1008 (Ortho Pharma), ¶[0001]. Ortho Pharma further states:

Due to the advantageous active ingredients of *the carotenoid-containing product, it can also be used as a food, in particular a food supplement*, in

the context of nutritional counseling. Preferably, the food, in particular food supplement, comprises the aforementioned active ingredients. Preferably, the carotenoid-containing product can be used as a nutritive supplement for adjunctive or supportive administration. ***It has been shown that in particular age-related eye diseases such as age-related macular degeneration or senile cataract can be positively influenced by diet.***

EX1008 (Ortho Pharma), ¶[0054].

198. Accordingly, it is my opinion that Ortho Pharma discloses a nutraceutical composition and that Claim 27 is obvious over Olsen 1988 and Ortho Pharma.

XIII. [GROUND 3] CLAIMS 7, 24 AND 26 ARE OBVIOUS OVER OLSON 1988 IN VIEW OF ORTHO PHARMA AND FURTHER IN VIEW OF WIDDER

199. For at least the reasons set forth below, each of claims 7, 24 and 26 of the '432 patent is obvious as a whole. The obviousness of these claims is exemplified by disclosures in the Olson 1988, Ortho Pharma, and Widder references.

200. The analysis provided for Ground 3 incorporates my analysis of Olson 1988 in Grounds 1 and 2 above in Sections XI-XII above. As I explained above, Olson 1988 discloses making and purifying the claimed C₂₀-D₁₋₃-retinoids. My analysis for Ground 3 also incorporates my analysis of Ortho Pharma for Ground 2 in Section XII above. As discussed above, Ortho Pharma discloses formulating vitamins (e.g., vitamin A, vitamin E, vitamin D, etc.), minerals, and other ingredients in a pharmaceutically acceptable carrier (e.g., water).

201. The teachings of Widder are added to Ground 3. Widder discloses additional agents and routes of administration for delivery of agents for treating eye diseases, such as macular degeneration (EX1009 (Widder), 2:25-28), the same goal of administering vitamin A disclosed in Ortho Pharma.

202. My analysis below shows that Olson 1988, Ortho Pharma, and Widder render each of claims 7, 24, and 26 obvious.

A. Claim 24: Phospholipids

24. The pharmaceutical composition according to claim 21, wherein the negatively-charged phospholipid is selected from the group consisting of cardiolipin, phosphatidylglycerol, and combinations thereof.

203. Claim 24 is directed to a pharmaceutical composition of claim 21 (which indirectly relies on claim 1), further comprising an additional active of a negatively-charged phospholipid selected from cardiolipin, phosphatidylglycerol, and combinations thereof. I explained above in Section XII.A that claim 1 is obvious over Ortho Pharma and Olson 1988. I also explained in Section XII.J that claim 21 is obvious over Olson 1988 and Ortho Pharma. Widder discloses the additional limitation of claim 24.

204. For example, Widder encourages the use of negatively-charged phospholipids in patients suffering from macular degenerations. EX1009 (Widder), 33:1-7 (stating that “[t]he use of certain negatively-charged phospholipids has also been shown to benefit patients with macular degenerations and dystrophies.”)

(citing EX1020-EX1021). Widder specifies that cardiolipin and phosphatidylglycerol are suitable negatively-charged phospholipids. EX1009 (Widder), 6:7-8 (stating “[t]he additional agent is a negatively charged phospholipid, including embodiments in which the negatively charged phospholipid is *phosphatidylglycerol*.”), 33:3-5 (stating “[e]xamples of suitable negatively charged phospholipids that could be used in combination with at least one compound having the structure of Formula (I) include *cardiolipin* and *phosphatidylglycerol*.”). Shaban (EX1021), cited by Widder, showed that phosphatidylglycerol inhibited A2E-mediated apoptosis in cultured human RPE cells. EX1020 (Shaban & Richter), Abstract (“Cell death induced by A2E in the dark is prevented by negatively charged phospholipids.”); EX1021 (Shaban et al.), Abstract (“Phosphatidylglycerol, a negatively charged phospholipid and immediate biosynthetic precursor of cardiolipin readily inhibits apoptosis.”). Widder thus discloses the additional limitation of claim 24. My analysis applied above in Ground 2, discussing the scope of claim 1, the differences between what is claimed and the prior art, and the level of skill in the art are applicable here. *See* Sections XII.A.a-c.

205. A person of ordinary skill in the art would have good reason to add a negatively-charged phospholipid to the pharmaceutical composition of claim 1 in order to treat or prevent macular degeneration, since Widder provides that

negatively-charged phospholipids have “shown to benefit patients with macular degenerations.” EX1009 (Widder), 33:1-7. A person of ordinary skill in the art would have good reason to select cardiolipin, phosphatidylglycerol, or a combination thereof because Widder identifies these agents as “suitable negatively charged phospholipids.” EX1009 (Widder), 33:3-5. Accordingly, it is my opinion that claim 24 as a whole is obvious over Olson 1989, Ortho Pharma, and Widder.

B. Claim 26: Ocular Administration

26. The pharmaceutical composition according to claim 1, wherein the pharmaceutical composition is suitable for administration directly to the eye.

206. Claim 26, reproduced above, is directed to a pharmaceutical composition of claim 1 that is suitable for administration directly to the eye. The ’432 patent clarifies that “suitable for administration directly into the eye” may include ophthalmic dosage forms, such as “eye drops, ointment, or injection.” EX1001, 9:55-58; EX1002, ¶254. I explained above in Section XII.A that claim 1 is obvious over Olson 1988 and Ortho Pharma. Widder discloses the additional limitation of claim 26.

207. Widder discloses treating ophthalmic conditions, such as macular degeneration and Stargardt disease, through multiple routes of administration, such as by ophthalmic delivery (“local delivery to the eye”), including using aqueous eye drops and other aqueous ophthalmic solutions, ophthalmic suspensions,

ophthalmic ointments, and ophthalmic injections. EX1009 (Widder), 25:20-24 (stating that “‘ophthalmic administration’ encompasses, but is not limited to, intraocular injection, subretinal injection, intravitreal injection, periocular administration, subconjunctival injections, retrobulbar injections, intracameral injections (including into the anterior or vitreous chamber), sub-Tenon’s injections or implants, ophthalmic solutions, ophthalmic suspensions, ophthalmic ointments, ocular implants and ocular inserts, intraocular solutions...”), 25:36-37 (stating that “[u]seful compositions can be an aqueous solution, suspension or solution/suspension, which can be presented in the form of eye drops. A desired dosage can be administered via a known number of drops into the eye.”). Widder thus discloses the additional limitation of claim 26.

208. Widder also discloses a pharmaceutical composition for treating ophthalmic conditions comprises a pharmaceutically acceptable carrier that is suitable for ophthalmic administration. EX1009 (Widder), 8:1-9 (stating that “the pharmaceutically acceptable carrier is suitable for ophthalmic administration...”). Additionally, and similar to the ’432 patent, Widder teaches that the pharmaceutical composition can be formulated in a conventional manner and cites Remington’s Pharmaceutical Sciences when discussing “well-known techniques, carriers, and excipients” for formulating and administering the pharmaceutical composition. EX1009 (Widder), 25:11-15 (“Pharmaceutical compositions may be

formulated in conventional manner using one or more physiologically acceptable carriers....Any of the well-known techniques, carriers, and excipients may be used as suitable and as understood in the art; e.g., in Remington's Pharmaceutical Sciences, above.").

209. As such, Widder discloses a pharmaceutical composition comprising a pharmaceutically acceptable carrier that is suitable for administration directly to the eye.

210. This disclosure by Widder falls within the scope of the additional disclosure of claim 26 of the '432 patent. For example, the '432 patent states that administration of eye drops and eye injections fall under the scope of "administration directly to the eye," as recited in claim 26. To illustrate, the '432 patent states:

... the present invention is a method of retarding formation of A2E. This method includes the step of replacing an all-trans-retinal (ATR) substrate with a Co-D-retinoid substrate under conditions sufficient to impede the formation of A2E. The replacing step in the last two embodiments may be accomplished using known method, including the methods disclosed above. For example, the substrate replacement may take place in the eye of the patient, e.g., *the substrate may be administered directly to the eye via eye drops, ointment, or injection.*

EX1001 (the '432 patent), 9:49-58.

211. My analysis applied above in Ground 2, discussing the scope of claim 1, the differences between what is claimed and the prior art, and the level of skill in the art are applicable here. See Sections XII.A.a-c.

212. A person of ordinary skill in the art would have had good reason to formulate a pharmaceutical of claim 1 for administration directly to the eye, since Widder provides that “[a]dministration of a composition to the eye generally results in direct contact of the agents with the cornea, through which at least a portion of the administered agents pass.” EX1009 (Widder), 25:26-27. A person of ordinary skill in the art would understand that local administration of the compound would allow concentration of the active agent in the target tissue. The reason for administering the pharmaceutical composition was to deliver C₂₀-deuterated vitamin A to the eye to allow the C₂₀-deuterated vitamin A to function normally within the visual cycle and to reduce lipofuscin formation. *See* Section XII.A.c.

213. As such, a person of ordinary skill in the art had good reason to formulate the pharmaceutical composition of claim 1 for administration directly to the eye.

214. Accordingly, it is my opinion that claim 26 is obvious over Olson 1988, Ortho Pharma, and Widder.

C. Claim 7: Supplement

7. The pharmaceutical composition according to claim 1, further comprising an effective amount of a supplement selected from the group consisting of (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-cis-retinoic acid, all-trans-retinylamine, and fenretinide, and combinations thereof.

215. Claim 7 of the '432 patent is directed to a pharmaceutical composition of claim 1 further comprising a supplement selected from the group consisting of (2E,6E)-N-hexadecyl-3,7,11-trimethyldodeca-2,6,10-trienamine, (12E,16E)-13,17,21-trimethyldocosa-12,16,20-trien-11-one, 13-cis-retinoic acid, all-trans-retinylamine, and fenretinide, and combinations thereof. I explained above in Section XII.A that claim 1 is obvious over Ortho Pharma and Olson 1988. Widder discloses the additional limitation of claim 7. Widder discloses a pharmaceutical composition comprising fenretinide. For example, Widder discloses effective doses of fenretinide for use in inhibiting the development or reoccurrence of macular degeneration. EX1009 (Widder), 40:3-5.

216. Furthermore, Widder discloses a combination therapy with fenretinide and vitamin A. For example, Widder discloses combination therapy with fenretinide and vitamin A for inhibiting the development or reoccurrence of macular degeneration. EX1009 (Widder), 47:21-27 (Example 15). Widder thus discloses the additional limitation of claim 7.

217. My analysis applied above in Ground 2 discussing the scope of claim 1, the differences between what is claimed and the prior art, and the level of skill in the art are applicable here. *See* Sections XII.A.a-c.

218. A POSA had a good reason to add fenretinide as a supplement to a pharmaceutical composition comprising C₂₀-deuterated vitamin A, since fenretinide acts by retarding the delivery of vitamin A into the eye from the blood stream and would reduce the amount of non-deuterated analogs of vitamin A in the eye from competing with C₂₀-deuterated vitamin A for use in the visual cycle. *See* Section VIII.B.

219. As such, a person of ordinary skill in the art had good reason to formulate the pharmaceutical composition of claim 1 further comprising fenretinide.

220. Accordingly, it is my opinion that claim 7 is obvious over Olson 1988, Ortho Pharma, and Widder.

XIV. NO UNEXPECTED RESULTS

221. It is my opinion that in view of the prior art there were no unexpected results presented in the '432 patent or during the prosecution of the '432 patent or its parent application. Though the patent applicant argued that lipofuscin formation was slowed up to 7 times by deuterating carbon-20 of vitamin A, Dr. Guengerich explains that this was an expected result of deuteration at carbon-20 of vitamin A

attributable to the well-known kinetic isotope effect. EX1002, ¶¶94-118, 170-186, 218-222, 335-340. Moreover, the prior art discloses C₂₀-deuterated vitamin A. See Section X.A above. As I explained above when analyzing claims 5-6 and 28 in Sections XI.D and XII.D, the patent attributes slowed lipofuscin formation entirely to the C₂₀-deuteration of vitamin A that was already disclosed in the prior art. From the standpoint of a clinician, there is no reason to attribute these results to any other factor. Nor were the effects of carbon-20 deuteration of vitamin A upon A2E and lipofuscin formation unexpected, because Mata (EX1010, Fig. 5) had demonstrated the importance of the C-20 position in dimerization and A2E formation, as discussed by Dr. Guengerich. EX1002, ¶¶87-93, 170-186, 231-34, 311-13; *see also id.*, Sections VIII.B, IX.E (discussing Mata), XIV. Accordingly, I conclude that reduced lipofuscin was not an unexpected result and flowed naturally from what was already disclosed in the prior art.

XV. CONCLUDING STATEMENTS

222. In signing this declaration, I understand that the declaration will be filed as evidence in a contested case before the Patent Trial and Appeal Board of the United States Patent and Trademark Office. I acknowledge that I may be subject to cross-examination in this case and that cross-examination will take place within the United States. If cross-examination is required of me, I will appear for

cross-examination within the United States during the time allotted for cross-examination.

223. I declare that all statements made herein of my knowledge are true, and that all statements made on information and belief are believed to be true, and that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code.

Dated: December 18, 2023

By: / Dr. Andrew Calman, M.D., Ph.D. /
Dr. Andrew Calman, M.D., Ph.D.

XVI. APPENDIX – LIST OF EXHIBITS

Exhibit No.	Description
1001	U.S. Patent No. 9,486,432 to Washington et al.
1002	Declaration of Dr. F. Peter Guengerich, Ph.D.
1003	<i>Curriculum Vitae</i> of Dr. Guengerich.
1005	<i>Curriculum Vitae</i> of Dr. Calman.
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”)
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